AD_____

Award Number: DAMD17-01-1-0677

TITLE: Enabling Technologies for Advanced Soft Tissue Modeling

PRINCIPAL INVESTIGATOR: Steven L. Dawson, M.D.

CONTRACTING ORGANIZATION: Massachusetts General Hospital
Boston, MA 02114-2554

REPORT DATE: September 2004

TYPE OF REPORT: Annual

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

DISTRIBUTION STATEMENT: Approved for Public Release;
Distribution Unlimited

The views, opinions and/or findings contained in this report are those of the author(s) and should not be construed as an official Department of the Army position, policy or decision unless so designated by other documentation.

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 074-0188

1. AGENCY USE ONLY (Leave blank)	2. REPORT DATE	3. REPORT TYPE AND DATES COVERED
	September 2004	Annual (1 Sep 2003 - 31 Aug 2004)

4. TITLE AND SUBTITLE
Enabling Technologies for Advanced Soft Tissue Modeling

5. FUNDING NUMBERS
DAMD17-01-1-0677

6. AUTHOR(S)

Steven L. Dawson, M.D.

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)

Massachusetts General Hospital
Boston, MA 02114-2554

E-Mail: dawson.steven@mgh.harvard.edu

8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)
U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

10. SPONSORING / MONITORING AGENCY REPORT NUMBER

11. SUPPLEMENTARY NOTES

12a. DISTRIBUTION / AVAILABILITY STATEMENT
Approved for Public Release; Distribution Unlimited

12b. DISTRIBUTION CODE

13. ABSTRACT (Maximum 200 Words)

Soft tissue properties represent a major and significant unknown in the domain of medical modeling and simulation. This program presents a 4-year research effort in defining tissue characteristics of three distinct organs (liver, spleen, and kidney) *in vivo*.
Over the course of this program, we will use novel methods of tissue interrogation to characterize non-linear behavior during slow deformations, as would commonly be seen during surgical manipulations. We will then develop mathematical models that can be optimized to permit near real-time representations of organ behaviors, including the boundary characteristics of organs *in situ*.
Year 3 has seen: the beginning of the motorization of our large deformation indenter; data showing that our perfusion system supports tissue so that *in vitro* tests closely approximate *in vivo* tests; indications that we can capture and distinguish properties of the organ capsule and parenchyma with our small and large indentation devices,; development of a hybrid large-deformation and 3-D ultrasound scanning technique; FEM implementing a variety of non-linear constitutive laws; an image-based system for studying "knife-edge" plane strain deformation of tissues; extended gel phantom work from year 2 including international collaborations; acquisition of external funding to extend the vocal tissue measurement work from year 2.

14. SUBJECT TERMS
tissue modeling; medical modeling and simulation; surgical training; mathematical modeling

15. NUMBER OF PAGES
48

16. PRICE CODE

17. SECURITY CLASSIFICATION OF REPORT	18. SECURITY CLASSIFICATION OF THIS PAGE	19. SECURITY CLASSIFICATION OF ABSTRACT	20. LIMITATION OF ABSTRACT
Unclassified	Unclassified	Unclassified	Unlimited

Table of Contents

Introduction

Computer-based medical modeling and simulation offers the potential for a completely new way to learn medical care. The use of computers as human assistants for medical diagnosis and training will require new knowledge domains. The most fundamental among these is the digital characterization of biophysical properties of perfused organs obtained from *in vivo* measurements, accounting for tissue properties integral to the organ as well as boundary conditions which affect the organ's global behavior.

Our research program is designed to obtain measurements of living tissue–liver, spleen and kidney–from large animal models and to use this data to characterize non-linear behavior during large-scale deformations, as would be seen in clinical practice. We are designing instruments to measure tissue properties and then creating mathematical models to allow representation of these data in a computer simulation.

The third year of the research has seen: further improvements to our test equipment, including the beginning of the motorization of our large deformation indenter; collection of data showing that our perfusion system does indeed support tissue so that *in vitro* tests can be made that closely approximate those made *in vivo*; produced indications that with our small and large indentation devices, we will be able to capture and distinguish properties of the organ capsule and parenchyma; developed a hybrid large-deformation and 3-D ultrasound scanning technique which will improve our ability to determine tissue models and properties uniquely; created finite element models implementing a variety of non-linear constitutive laws; and introduced an image-based system for studying "knife-edge" plane strain deformation of tissues. In addition, we have extended the work on the gel phantoms (Truth Cubes) that we began in year 2, as a simple model to support our imaging efforts.

Finally, the work towards measuring the material properties of vocal tissues in year 2 led to additional funding to develop a dedicated instrument for this purpose, which was substantially completed in year 3.

All work has been done according to institutional- and Defense Department-approved animal studies protocols.

Body

The following sections present our third year results organized according to the Statement of Work from our original research proposal. The points in that Statement include:

- Refine indentation testing and uni-axial tension testing of component tissues
- Measure 2-D properties of capsules and vessels
- Integration of FEM into component models
- Whole organ animal in-vivo indentation and implanted device testing with imaging for boundary conditions
- Initial FEM of whole organ indentation studies
- Initial testing on resected (*ex vivo*) human tissue

In addition to the aforementioned points, the following were also commenced, accomplished or continued from year two:

- Optical Imaging-based Testing Technique
- Concluded the initial phase of development of the perfusion system to establish the optimal perfusion protocol
- Extended the work on the "Truth Cube" by developing an axisymmetric version of the standard phantom (the Truth Cube 2, or TC2) which includes fiducial markers made primarily of the same material as the phantom, and a new material which is still linearly elastic, but is more robust than the silicone gel used for the first Truth Cube.
- Established an international collaboration to analyze different testing techniques applied to the TC2 and extract material parameters based on each technique.

Refine indentation testing and uniaxial tension testing of component tissues

Ideally, to obtain accurate soft tissue material properties, testing would be done in an environment natural to the tissue being tested, and in a manner under which all the boundary and loading conditions of the measurement apparatus can be carefully controlled. However, these are normally not mutually compatible. Thus in year two, we developed a perfusion apparatus that mimicked the natural *(in vivo)* conditions of whole porcine liver while allowing us to test the organ in a controlled laboratory setting free from physiological noise, accessibility issues, and reducing ethical concerns. To validate this system in year three, we compared measurements across four different environmental conditions using two different indentation devices.

In year three, the manual, large deformation indentation tester was modified so that it could be used in an open surgical, *in vivo* setting to measure the response of porcine liver (and in principle, spleen). This involved developing a supporting plate on which the living organ rests during testing, to provide a fixed reference for measuring indentation depth (see Figure 1).

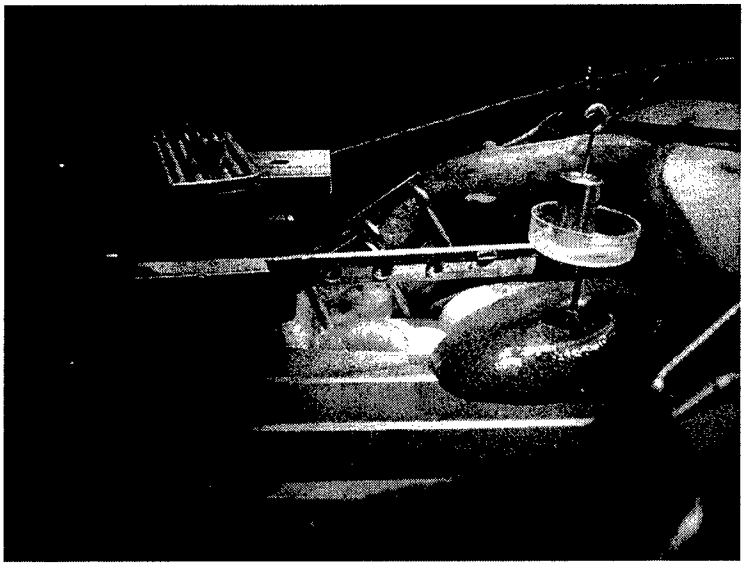

Figure 1: Large deformation indenter modified for in vivo use. Note platform with non-slip surface underneath organ tissue.

With this new capability, large deformation, *in vivo* measurements on porcine liver were conducted, followed by measurements on the same tissues in the perfused and unperfused states, as well as separate measurements on liver lobes that had been excised but otherwise left untreated. This latter case provided a basis for comparison between perfused tissues and tissues left untreated (which is often the case in much of the available literature).

In parallel with the large deformation tests on tissue under these different conditions, small deformation, high frequency tests (using the TeMPeST instrument, described in previous reports) were conducted on the same tissues, in the same locations, so that data would be available to develop extended models based on data over a wide range of loading and time scales. In a number of cases, multiple locations on the same organ were examined to provide data on variation in properties within the same organ (see Figure 2)

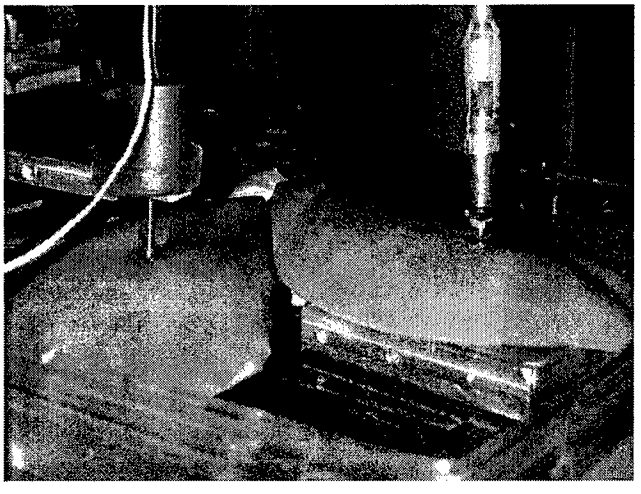

Figure 2: Large strain creep indenter (left) and TeMPeST (small strain high frequency indenter, right) on a perfused in vitro porcine liver.

We took histological samples during the perfused tests to determine whether we were maintaining the mechanical and structural integrity we desired. Results read by an experienced pathologist indicate that although some changes had occurred (namely due to our perfusate pressures and composition), we did maintain mechanical integrity. We have continued to refine our perfusion system and establish a protocol for future testing, having determined the proper perfusate pressures, composition and temperatures.

We have decided to not use tensile testing as an additional measurement modality but rather knife-edge indentation (see Optical Imaging-based Testing Technique section below), since tissues are more often manipulated and probed in compression than in tension.

Measure 2-D properties of capsules and vessels

The side by side measurements of the small strain high frequency TeMPeST device and the large strain creep device have suggested that by combining the results from the two devices we can pull out both capsule and parenchymal properties. Modeling of the TeMPeST results suggests that the tissue is a first order linear visco-elastic material. The large strain device data fits best to a second order model suggesting a stronger viscous response and nonlinear elastic behavior. We believe that the former is capturing mainly capsule information and so subtracting its results from the larger strain data will result in parenchymal properties.

The vessel data derived from tactile imaging in last year's report suggest that the perfusion pressure dominates the vessels' contribution to the organs properties versus the presence of the vessels themselves. Similarly, the initial modeling (described in the next section) of the large strain data suggest that the perfusion component can not be ignored. Thus we feel that the vessels can be incorporated into the parenchymal model versus being addressed separately.

Integration of FEM into component models

As the research has evolved, the modeling effort has been consolidated, and all details regarding finite element modeling are described below.

Whole organ animal in-vivo indentation and implanted device testing with imaging for boundary conditions

Seven tests were done on porcine livers to develop the perfusion apparatus, compare testing environments, and collect initial data using one or the other testing device. As indicated above, whole organ, *in vivo* testing has been commenced, and four complete data sets, including testing with both the large and small indentation instruments, under all four conditions (*in vivo*, perfused, unperfused and excised section) have been collected.

We have shown that the early perfusion protocol produced responses intermediate between the *in vivo* and the untreated or unperfused tissue (see Figure 3). This means that we have a bench top system that approaches the condition of organs *in vivo*, enabling more convenient tissue testing (compared with doing so in the operating room) and the acquisition of high quality data relevant to our applications including surgical simulation in particular.

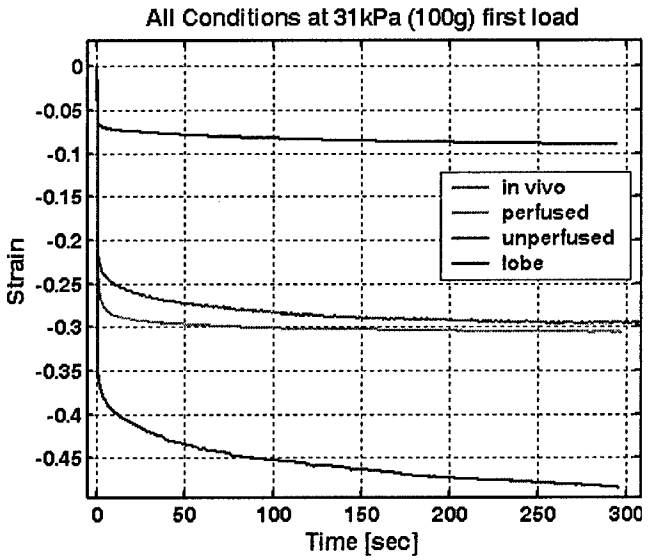

Figure 3: Representative data set of all 4 conditions tested on 1 liver using the large strain creep device. Note the similarities between both the shape of the curve and the steady state response for the perfused and in vivo state versus the excised (lobe) and unperfused states.

We have investigated the use of 3-D ultrasonic imaging in conjunction with large strain indentation testing to obtain boundary condition information and 3-D internal volumetric displacement fields for both constitutive law development and whole organ validation. Being able to image the internal structures of the liver allows us to better place the indentation probe

over a homogenous region (i.e. away from major vessels hidden beneath the surface of the liver). A 3-D optical flow algorithm based on the technique of Horn and Schunck has been developed, allowing us to obtain the 3-D flow field of internal tissue displacement from a sequence of ultrasonic volumes. In other words, we can estimate the volumetric displacement field of the tissue over time when subjected to large indentations. Initial modeling has been done that suggests that this additional data is useful in determining the unique material parameters we seek. We have adapted the large strain testing apparatus to include the 3-D US scanner head below the surface of the tissue so that images can be made in conjunction with the indentations (Figure 4). Initial data sets are currently being analyzed. Lastly, it is our hope to use 3-D US in conjunction with other imaging modalities to validate the whole organ model.

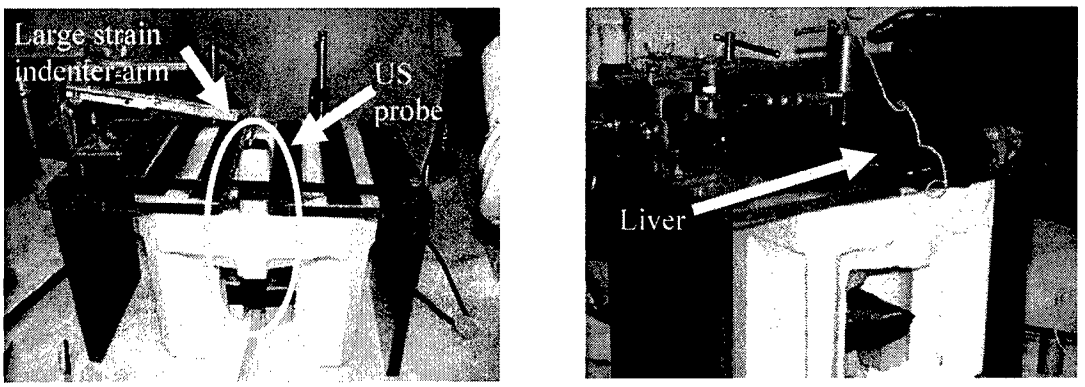

Figure 4: (Left) New platform set-up for large strain creep measurements with 3-D US probe. (Right) Porcine liver being loaded and imaged simultaneously *in vitro*.

As discussed in the year 2 annual report, we have moved away from the use of the implantable T-needle parenchymal testing system in favor of our various indentation techniques. We continue to plan additional testing techniques with simpler instrument-tissue interaction geometries to enable collection of vessel and other tissue type properties.

Initial FEM of whole organ indentation studies

We have developed a finite element model mesh of an indenter and soft tissue. We have investigated the various nonlinear hyperelastic constitutive models currently available in ABAQUS. From this investigation we have discovered that the behavior of the perfused liver can not be modeled using standard constitutive models, and that a more physiologically based model is required.

A collaboration has been established with a soft tissue modeling expert at MIT. We will be using a constitutive model developed for cervical tissue (Febvay 2003) and adapted for the liver. This model allows for the contribution of each of the components of interest. The goal is to have the response from our testing devices modeled by the association in parallel of a nonlinear elastic 8-chain model network, accounting for the role of the interlobular septa, and a viscoelastic component, representing the hydrated ground substance. The transient effects associated with fluid flow are accounted for in terms of a linear Darcy's law. The complete three-dimensional model resulting from these components will be implemented as a user material subroutine for ABAQUS 6.4. (see Figure 5).

We are currently working on understanding this model and adapting it to liver tissue based on our measurements.

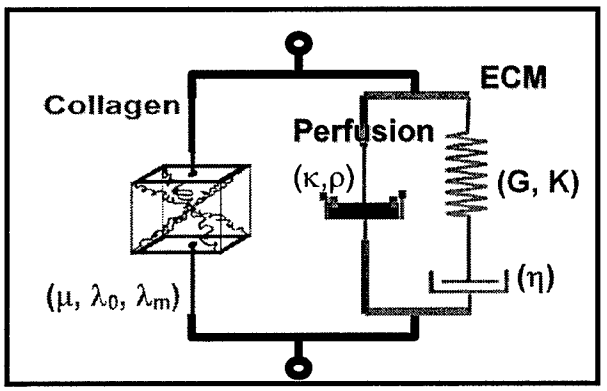

Figure 5: Schematic of constitutive model representing the nonlinear elastic collagen component in parallel with components for perfusion and the ground substance. All together, we believe this model represents the parenchyma and vasculature of the liver.

Initial testing on resected (*ex vivo*) human tissue

When proposed, our research did not anticipate the development of the perfusion system, which would greatly improve the quality of data obtained from tissue in general, and human tissue in particular. As such, since we have only recently determined the proper test protocol for using the perfusion system, no human tissue tests have been performed to date. We anticipate approaching this goal in year four.

Optical Imaging-based Testing Technique

Last year we introduced a method for inducing plane strains on a whole organ surfaces using knife-edge indentation and analyzing the shape of the tissue's surface using a digital camera. We furthered this effort in year 3 by developing a gel that had a more realistic shape, size, and color of liver, inducing plane strains in a controlled manner on these gels, and obtaining accurate digital images of the surface curvature. The experimental set-up was modeled in ABAQUS to determine whether we can obtain useful material property information from surface curvature given a known displacement. Results suggest that with a few minor modifications, this knife-edge indentation might be able to be used as a second testing modality to validate the constitutive laws developed from the cylindrical indentation testing equipment (small strain TeMPeST and large strain creep indentor).

Truth Cube 2: ongoing work on silicone phantoms

The work commenced in year 2 on the Truth Cube has been very well received and generated much interest in the medical simulation/soft tissue modeling community. The original Truth Cube was a silicone gel cube, 8cm on a side, with fiducial beads placed in a 3-D grid pattern within the gel. It was CT scanned while undergoing uniform compression and indentation with a hemispherical punch. The motion of the fiducial beads allowed the calculation of the 3-D strain field within the Cube. This data set provides a gold standard against which both finite element and real time deformation algorithms can be compared.

As a result of the publication of this work, other groups became interested in obtaining new phantoms so that they could compare the results of deformations made by their own soft tissue measurement instruments with those made by other groups. We created a series of new

Truth Cubes, now in cylindrical, axisymmetric form, with randomly scattered fiducials, and made of a different, more robust gel material that still retains the linear-elastic constitutive law of the original Truth Cube. We have tested them with the TeMPeST small-deformation instrument and distributed them to our collaborator Prof. Edoardo Mazza (ETH, Zurich), who will test them with a suction-testing device. He will then forward them to colleagues at Nagoya University in Japan and at Brown University, who have developed additional testing techniques. We anticipate being able to present results of the comparisons as well as the results of Mazza's calculation of material parameters, as his group has developed a semi-automated algorithm for determining parameters from experimental data.

Key Research Accomplishments

- Modified large deformation instrument to support *in vivo* data collection (formerly benchtop *in vitro* only)
- Collected 11 data sets on porcine liver: 4 under all conditions with both instruments, 7 under selected conditions with one or both instrument
- Had histological analysis performed on tissue samples to examine time sequence of changes in tissue structure across condition
- Showed that the perfusion system does maintain tissue mechanical response equivalent to the *in vivo* state
- Showed differences between large and small indentation testing, enabling isolation of material properties of capsule and parenchyma
- Determined through modeling that vessels may be modeled as part of the parenchyma, as the internal perfusion pressure governs behavior, more than the presence or absence of vessels
- Developed instrumentation to perform combined large deformation and 3-D ultrasound scanning tests, combining imaging and mechanical testing techniques
- Created finite element models of tissues, and examined various non-linear soft tissue constitutive models. Selected and modified an advanced model originally developed for cervical tissue
- Extended the optical imaging/knife-edge plane strain testing technique introduced in year 2 by improving the gel models and image analysis system
- Introduced a new version of the Truth Cube (developed in year 2) and entered into an international collaboration to examine additional testing and analysis techniques
- Acquired funding to extend vocal soft tissue research towards the development of a dedicated instrument for eventual *in vivo* measurements.

Reportable Outcomes

Conference papers

- Kerdok, A. E., Socrate, S. & Howe, R. D. 2004 Soft Tissue Modeling and Mechanics. In *American Society of Biomechanics Annual Meeting 2004* (ed. M. Bottlang & S. M. Madey). Portland, OR. (poster presentation)
- Ottensmeyer, M. P., Kerdok, A. E., Howe, R. D. & Dawson, S. L. 2004 The Effects of Testing Environment on the Viscoelastic Properties of Soft Tissues. In *Second International Symposium on Medical Simulation* (ed. S. Cotin & D. Metaxas), pp. 9-18. Boston, MA: Springer Verlag. (oral presentation)
- Liu, Y., Kerdok, A. E. & Howe, R. D. 2004 A Nonlinear Finite Element Model of Soft Tissue Indentation. In *Second International Symposium on Medical Simulation* (ed. S. Cotin & D. Metaxas), pp. 67-76. Cambridge, MA: Springer Verlag. (poster presentation)
- A.E. Kerdok, R.D. Howe: "The Effects of Testing Environment on Soft Tissue Properties". MIT Health Sciences and Technology 2004 Forum Abstract.

Invited lectures/workshops/meetings

- M.P. Ottensmeyer, "Biomedical Engineering," Shad Valley Program guest lecture, Dalhousie University, Halifax, Canada, 2004.
- S.L. Dawson, M.P. Ottensmeyer, A.E. Kerdok, R.D. Howe, "Enabling Technologies for Advanced Soft Tissue Modeling," presented at PRMRP Military Health Research Forum, San Juan, PR, 2004. Poster and oral presentations

Conclusions

As was done in year two, significant progress was made towards our goal of developing advanced techniques to determine the behavior of soft biological tissues. The learning experiences of the previous years have led to the collection of new data and extraction of useful tissue property parameters, and have guided the research in interesting new, and sometimes unexpected directions.

With respect to instrumentation, the large deformation indenter continues to evolve and it can now be used not only *in vitro*, but also in the operating room during open animal surgery, as well as on the bench top in conjunction with the 3-D ultrasound scanning system. This enables not only the force/displacement mechanical testing that we had developed previously, but also estimation of the internal strain field of the tissue as it is deformed. This additional data has been shown to allow improved estimation of unique parameters and model selection (whereas mechanical testing alone could not). The strain field calculations are made using algorithms adapted specifically for use with our system. Finally, the optical imaging/knife-edge test has been refined and the gel phantoms that we are employing to validate this system have been improved to more closely match the physical and optical character of liver tissues.

In addition, our perfusion system continues to be improved, both in reliability and in the specific protocol that we employ to support the mechanical behavior of the tissues in the first few hours *post mortem*. In our year 4 research, only minor changes to the protocol are anticipated.

Data collection has now grown to partial data sets for eleven porcine livers, of which four cover measurements made under all test conditions (*in vivo*, perfused, unperfused and excised section) and with both the large and small indenters. These data show that the characteristic time constants measured with the large indenter are nearly the same under *in vivo* and perfused conditions, and are different from the parameters for the unperfused and lobe data, which, because they are not maintained in a homeostatic condition, progressively change over time. The small indentation data are beginning to show that for very small indentations, we are measuring primarily the response of the organ capsule, while deeper tests show significant contributions of both capsule and parenchyma, including the vasculature. This supports our early hypothesis that properties of both kinds of tissues could be extracted from whole organ tests, rather than requiring preparing (and likely altering) the tissues so that they could be tested separately.

Our modeling efforts are now in full swing, as we have developed finite element models of the tissues and begun to study the effects of using different constitutive relations to describe the underlying tissue behavior. One model in particular, developed to describe the complex behavior of cervical tissue, has been modified for use to describe the liver responses that we are measuring.

We continue to develop our linear gel material phantoms to serve as a simpler standard reference for development of 3-D ultrasound imaging tests, and comparison of our techniques with those employed by other soft tissue researchers around the world. The new version of the Truth Cube (now a cylinder) is an improvement over the original in that it is more resistant to damage (the original was destroyed during testing), has an axisymmetric geometry, which simplifies modeling and analysis, and now exists in multiple copies, so that both we and our collaborators may perform tests with our own instruments, on our own instances of the "Cube"

Departures from the proposal include the postponement of the development of vascular testing instrumentation and continued use of indentation techniques over the 2-D deformation tests that we proposed for determination of organ capsule and vessel properties. Mathematical models including the effects of perfusion at physiological pressure have shown that the contribution of the vessels to the mechanical behavior can be simplified to include only the parenchyma (provided the vessels remain intact). Thus, our goals of developing dedicated *in vivo* or whole organ vessel testing devices is less pressing than originally expected. Similarly, the results that we have obtained from indentation testing indicate that we may not need to perform 2-D testing of capsule to obtain its properties, since the indentation tests and modeling techniques will likely yield the same information. We also feel that the development of tension devices are not needed since the non load bearing tissues in this study are probed more often in compression than in tension. Thus we have developed a different testing modality in the "knife-edge" indenter. Finally, we have postponed our testing of human tissue samples because of the unanticipated development of the perfusion system and testing protocol for maintaining tissue properties. Given our new ability to maintain tissues in near *in vivo* conditions, we anticipate that planned human tissues measurements will be of higher quality than we could have expected prior to the development of the perfusion system.

"So what?"

The results and progress of year three indicate that we are well on track towards our goals of being able to characterize the *in vivo* mechanical behavior of biological tissues. The success of our perfusion system means that we can now use tissues harvested from other researchers' non-survival experiments immediately after animal sacrifice, and still acquire meaningful

material data. Our testing techniques continue to improve and expand, and the success of our work has and continues to attract the attention of other researchers in the field, an additional indication to us that we are asking the right questions and getting good answers.

We are close to the point where our tissue models and parameters can be implemented in other users' finite element or real-time models, and while they currently describe animal tissues, development can continue in those areas with the expectation that when human data are available, only minor revisions will be necessary to make use of such data.

One of the proposed goals of the research has been to be able to measure the responses and mathematically describe human soft tissues, up to the level of testing tissues removed during surgery, rather than performing *in vivo* tests. We will endeavor over the next year to approach, and hopefully to perform such testing. At the same time, we will realize plans for further research that will extend our efforts here beyond year 4, into the realm of developing systems that will enable limited *in vivo* human testing to validate the results of expected more extensive testing (based on the methods developed here) on harvested tissues.

Ultimately, these models and parameters will enable the development of virtual training systems that will minimize the use of animals for training, improve the skills of practitioners so that they are already more capable when they first enter an operating room, and even serve as surgical planning and new procedure development tools. Such systems will reduce the cost of medical training while simultaneously addressing growing animal-rights concerns. And the latter applications will benefit patients in terms of improved outcomes and potentially treatments for ailments that may currently be too difficult or dangerous to perform without the kind of pre-operative rehearsal that our research will help to enable.

REFERENCES:

Febvay, S. (2003). Massachusetts Institute of Technology. Master of Science.

Appendix A: Papers, Abstracts, Supporting Material

- Kerdok, A. E., Socrate, S. & Howe, R. D. 2004 Soft Tissue Modeling and Mechanics. In *American Society of Biomechanics Annual Meeting 2004* (ed. M. Bottlang & S. M. Madey). Portland, OR. (poster presentation)
- Ottensmeyer, M. P., Kerdok, A. E., Howe, R. D. & Dawson, S. L. 2004 The Effects of Testing Environment on the Viscoelastic Properties of Soft Tissues. In *Second International Symposium on Medical Simulation* (ed. S. Cotin & D. Metaxas), pp. 9-18. Boston, MA: Springer Verlag. (oral presentation)
- Liu, Y., Kerdok, A. E. & Howe, R. D. 2004 A Nonlinear Finite Element Model of Soft Tissue Indentation. In *Second International Symposium on Medical Simulation* (ed. S. Cotin & D. Metaxas), pp. 67-76. Cambridge, MA: Springer Verlag. (poster presentation)
- A.E. Kerdok, R.D. Howe: "The Effects of Testing Environment on Soft Tissue Properties". MIT Health Sciences and Technology 2004 Forum Abstract

SOFT TISSUE MODELING AND MECHANICS

Amy E. Kerdok[1, 2], Simona Socrate[1, 3], Robert D. Howe[1, 2]

[1]Harvard/MIT Division of Health Sciences and Technology, Cambridge, MA
[2]Biorobotics Laboratory, Harvard University Division of Engineering and Applied Sciences, Cambridge, MA
[3] Massachusetts Institute of Technology Dept. of Mechanical Engineering, Cambridge, MA
E-mail: kerdok@fas.harvard.edu

INTRODUCTION

Although most soft tissues do not have load-bearing functions, understanding their mechanical behavior is of great interest to the medical simulation, diagnostic, and tissue engineering fields. Obtaining these properties is a formidable challenge due to soft tissue's mechanical and geometric nonlinearities, multi constituent heterogeneity, viscoelastic nature and poorly defined boundary conditions.

It has been shown that the mechanical response of soft tissues drastically change when removed from their natural environment (Brown et al. 2003; Ottensmeyer et al. 2004). It is necessary to measure the tissue's mechanical response under *in vivo* conditions. Several groups have made measurements *in vivo* (Brown et al. 2003; Ottensmeyer 2001), but the interpretation of these results remain to be understood because of the inability to control boundary conditions and other testing parameters.

Using a method to maintain a nearly *in vivo* environment for *ex vivo* tests, we have measured the force-displacement characteristics of whole porcine liver using a motorized indenter. The results of these tests are to be interpreted using inverse finite element modeling. The material parameters will be determined from a constitutive model developed for cervical tissue (Febvay 2003) and adapted for the liver.

METHODS

To obtain nearly *in vivo* conditions in an *ex vivo* state, a perfusion apparatus developed by Ottensmeyer et al. (2004) was used. Pigs used were systemically heparinized, their livers were harvested and flushed of blood, placed on ice for transport to the lab, and connected via the portal vein and the hepatic artery to a perfusion apparatus within 90 minutes post sacrifice that maintained nonpulsatile physiologic pressure (9 mmHg and 100 mmHg respectively) and temperature (39°C).

Tests were performed to capture the viscoelastic nature of the tissue using the motorized "ViscoElastic Soft tissue Property Indenter" (VESPI). As a preliminary step to guide the device development large strain (~50%) creep tests were performed. The thickness of the tissue was measured prior to each load (to determine nominal strain), and the tissue was allowed to recover to its initial state before repeating the test in each location. Future tests will be performed to capture the complete viscoelastic tissue response including large strain stress relaxation tests and cyclic loading/unloading tests at varied strain rates.

An axisymmetric finite element model to analyze the indentation of soft tissue is being

developed using commercial finite-element software (ABAQUS 6.4, HKS, Rhode Island). This model will incorporate the constitutive model for liver tissue. The constitutive model reflects the tissue structure, as the global tissue response is controlled by the cooperative contributions of its major constituents. The response is modeled by the association in parallel of a nonlinear elastic 8-chain model network, accounting for the role of the interlobular septa, and a viscoelastic component, representing the hydrated ground substance. The transient effects associated with fluid flow are accounted for in terms of a linear Darcy's law. The complete three-dimensional model resulting from these components is implemented as a user material subroutine for ABAQUS 6.4.

The results of the VESPI tests and testing conditions will be used as inputs to the FEM containing the adapted constitutive model for liver tissue. An iterative process will ensue to determine the material parameters that uniquely identify the mechanical characteristics of the liver.

RESULTS AND DISCUSSION

Results from the preliminary large strain creep indentation tests using perfused *ex vivo* whole porcine livers are shown in Figure 1. These tests qualitatively reveal repeatable results within location over time, and a clear creep response where a steady state was achieved within 5 minutes.

The VESPI is currently being modified to operate under position control so that stress relaxation and ramp tests can be performed.

SUMMARY

This work presents preliminary results from large strain creep tests performed on *ex vivo* whole liver tissue using a perfusion system that mimics *in vivo* conditions. A description of the proposed constitutive model was also given. Future tests will obtain stress relaxation and hysteresis results as inputs for a finite element model that will be used to identify the mechanical parameters of the liver.

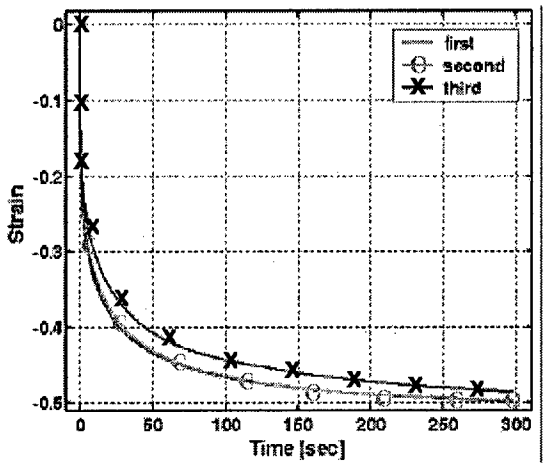

Figure 1: VESPI 100g-creep response on a 27kg perfused pig liver at the same location. The second and third indentations were taken 20 and 48 minutes after the first.

REFERENCES

Brown, J. D., Rosen, J., et al. (2003). *Proceedings of Medicine Meets Virtual Reality.*

Febvay, S. (2003). Massachusetts Institute of Technology. Master of Science.

Ottensmeyer, M. P. (2001). *Proceedings of Medical Image Computing and Computer-Assisted Intervention - MICCAI.*

Ottensmeyer, M. P., Kerdok, A. E., et al. (2004, accepted). *Proceedings of Second International Symposium on Medical Simulation.*

ACKNOWLEDGEMENTS

Supported by a grant from the US Army, under contract number DAMD 17-01-1-0677. The ideas and opinions presented in this paper represent the views of the authors and do not, necessarily, represent the views of the Department of Defense.

The Effects of Testing Environment on the Viscoelastic Properties of Soft Tissues

Mark P. Ottensmeyer[1], Amy E. Kerdok[2,3], Robert D. Howe[2,3], Steven L. Dawson[1,4]

[1]CIMIT Center for Surgical Simulation
[2] Harvard University Division of Engineering and Applied Sciences
[3] Harvard/MIT Division of Health Sciences and Technology
[4]Department of Radiology, Massachusetts General Hospital

1. Abstract:

Biological tissue mechanical properties are needed for accurate surgical simulation and diagnostic purposes. These properties change post-mortem due to alterations in both the environmental and physical conditions of the tissue. Despite these known changes, the majority of existing data have been acquired *ex vivo* due to ease and accessibility of testing. Various groups have studied whole and excised partial-organ soft tissue properties *in vivo*, *ex vivo* in a bath maintained at physiological temperature or untreated in a test apparatus, but very little data is available comparing the results in all of these cases with the same instrumentation on the same tissue. This study seeks to quantify the effects of testing conditions on the measurements obtained. We will discuss measurements made with indentation probes on porcine liver tissue *in vivo, ex vivo* with a perfusion system that maintains temperature and hydration with heparinized Lactated Ringer's solution at physiological pressures, the same tissue *ex vivo* unperfused, and untreated excised lobes from the same organs.

The data show >50% differences in steady state stiffness between tissues *in vivo* and unperfused, but only 17% differences between *in vivo* and perfused tests. Variations also exist in the time-domain and frequency domain responses between all test conditions.

Employing unperfused measurements as a proxy for *in vivo* data will result in significant inaccuracies in surgical simulators for training. Use of the current perfusion system provides conditions closer to the living state, enabling the use of freshly harvested organs from a variety of source for data collection. Improvements to the system are proposed based on these initial experiments.

Keywords: porcine liver, visco-elastic properties, perfusion, *in vivo*

2. Introduction/Motivation:

The mechanical properties of biological tissues are necessary for accurate surgical simulation and diagnostic purposes. Software-based simulation of surgical procedures relies on accurate representation of the mechanical response of tissues subject to surgical manipulations. If the tissue models or parameters are significantly different from reality, then negative training transfer may result from the use of the flawed simulator. Palpation, or manual evaluation of tissue mechanical response, has been used since the dawn of medicine, and numerous types of pathology cause changes in the visco-elastic character of tissue [1,2]. Should mechanical testing be used on this basis for diagnostic purposes, accurate measurements of healthy and diseased tissues are needed.

Soft tissues not only have complex material properties that are difficult to characterize, but also exist in an environment that effects their intrinsic behavior. Testing the tissue in its natural state is ideal for ensuring accurate representations of the mechanical behavior we wish to characterize but difficult to achieve due to accessibility, ethical, variability, noise, and uncontrolled boundary condition issues. Despite these issues, several groups have recently developed instrumentation to measure tissue properties

in vivo [3, 4, 5, 6, 7, 8]. Although these groups have successfully made force-displacement measurements on tissues *in vivo*, the interpretation of these results remains to be understood.

The majority of existing data has been acquired under *ex vivo* conditions because this allows for precise control of boundary and loading conditions, provides access to appropriate testing sites and uses fewer animals [9, 10, 11, 12]. However, testing soft tissues *ex vivo* drastically alters their properties and behavior [7, 13] and transplant researchers indicate that tissues lose their functional viability and structural integrity within hours [14, 15]. A qualitative and quantitative understanding of the differences in measuring material properties from these different conditions is clearly needed.

We believe that to best understand the differences between testing conditions, measurements that can capture both the elastic and viscous properties of soft tissues need to be made on the same organ, at the same location, across various environmental conditions. Although groups have made measurements in various environmental states [3, 5, 7] (*in vivo, in situ,* whole and partial organ *ex vivo* with and without controlling for hydration and temperature effects), no examples were found in which tissues were tested, harvested and retested in the same location with the same instruments to examine the changes in tissue properties *post mortem.*

This study seeks to quantify the effects of testing conditions on soft tissue material property measurements. We will discuss measurements made with two different indentation probes designed to capture the elastic and viscous material properties on whole porcine liver tissue *in vivo, ex vivo* with perfusion, *ex vivo* post-perfusion, and *in vitro* (i.e. warm ischemic partial organ tissue). These tests serve to verify the function of our perfusion system, examine the differences between *in vivo,* perfused and unperfused tissue, compare intact versus excised organ conditions.

3. Methods

We seek to quantify the responses of tissues under four different conditions, namely the *in vivo* case, the *in vitro* excised lobe case, and two different *ex vivo* whole organ cases including perfused testing, and testing on tissues that have been flushed of blood with the perfusate, but tested thereafter without being supported by the perfusion system.

The following sections describe the perfusion system in detail, as well as the indentation testing apparatus used to measure the visco-elastic response of the tissues under each test condition.

3.1 Normothermic Extracorporeal Liver Perfusion System

To accurately measure the mechanical properties of the liver, it is crucial that we maintain cellular integrity while keeping the organ in as natural a state as possible *ex vivo.* Thus we have built an apparatus similar in concept to normothermic extracoporeal perfusion systems using heparinzed Lactated Ringer's solution as the perfusate (see Figure 1). The system stores this solution in reservoirs suspended at specified heights to obtain the appropriate physiologic pressures into the hepatic artery (100-120mmHg) and portal vein (15-20mmHg). Both pressures and flow rates can be easily adjusted by altering the height of the reservoirs and by partially closing tubing clamps respectively. The perfusate is then allowed to drain via the intrahepatic vena cava into a bath where it is heated to a physiologic temperature (39C for pigs) and circulated to the reservoirs via a pump. The solution also flows over the organ to maintain hydration without having to submerge the organ. To ensure consistency in our measurements, the organ rests on a sturdy plate covered with fine grit sandpaper to localize and stabilize the area of tissue under study, and the perfusion pressure is held constant rather than mimicking physiologic pulsatile pressure.

3.2 Test Instruments

We used two different indentation devices to measure the viscoelastic response of the tissue. The TeMPeST (Tissue Material Property Sampling Tool) allows us to measure the small strain frequency

response of tissues, while the VESPI (Visco-Elastic Soft-tissue Property Indentation instrument) examines the large strain time-domain response (see Figure 2).

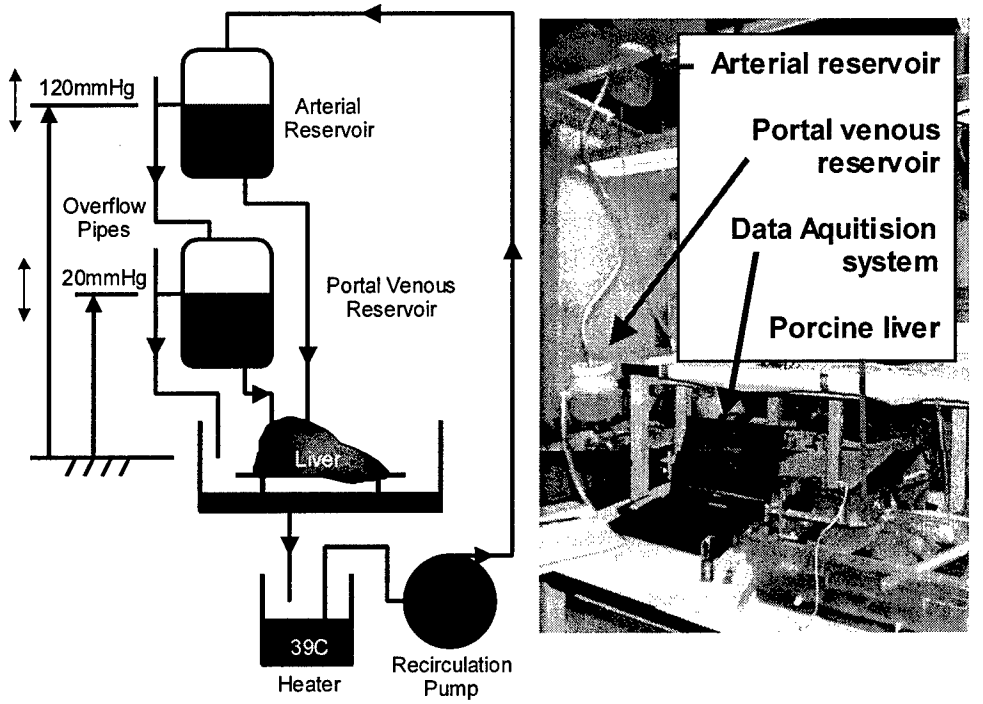

Figure 1: (left) Our Normothermic Extracorporeal Liver Perfusion system schematic. (right) NELP system in use.

3.2.1 TeMPeST 1-D

TeMPeST 1-D is a 12mm diameter minimally invasive instrument, designed to measure the compliance of solid organ tissues within the linear regime. A 5mm right circular punch vibrates the tissue while recording applied load and relative displacement. Mechanical bandwidth is approximately 80Hz when in contact with organ tissues, however the force and position sampling frequency is up to 2kHz, so measurements can be made to approximately 200Hz, depending on the material. Range of motion is 1 mm and forces up to 300mN can be exerted. It has previously measured the properties of porcine liver and spleen *in vivo*, rodent (rat) liver and kidney *ex vivo* [6, 16], and has been used in initial investigations of bovine, ovine and human vocal tissue samples *ex vivo*.

3.2.2 VESPI

The VESPI also performs normal indentation on tissues. It was designed for bench-top use, and subsequently modified to permit open surgical *in vivo* measurements as well. A 6mm diameter flat punch rests, with only 3g load due to counter weights, on the tissue surface until a standard laboratory mass is released (at zero velocity) onto a platform mounted co-axially with the indenter tip. The organ rests on the same platen to which the measurement arm and indenter tip are mounted. Loads from 20 to 100g (nominal stresses of 6.2 to 31kPa) generate much larger deformations than those created by the TeMPeST. Because of the large range of motion of the instrument, and the relative immobility of the organ resting on the platen (compared with TeMPeST testing), breathing does not need to be suspended during testing, enabling much longer data acquisition periods (typically 300 seconds). During this period, the angular position of the measurement arm is measured at a rate of 1kHz using a miniature contactless rotary position sensor (Midori America Corporation, CA) (resolution 13.7μm, signal to noise ~100:1).

Since the lever arm has a length of 11.5cm, and the maximum depth of indentation was on the order of 10mm, small angle approximation was assumed and thus the voltage from the rotary sensor is converted directly to indentation depth using a linear gain.

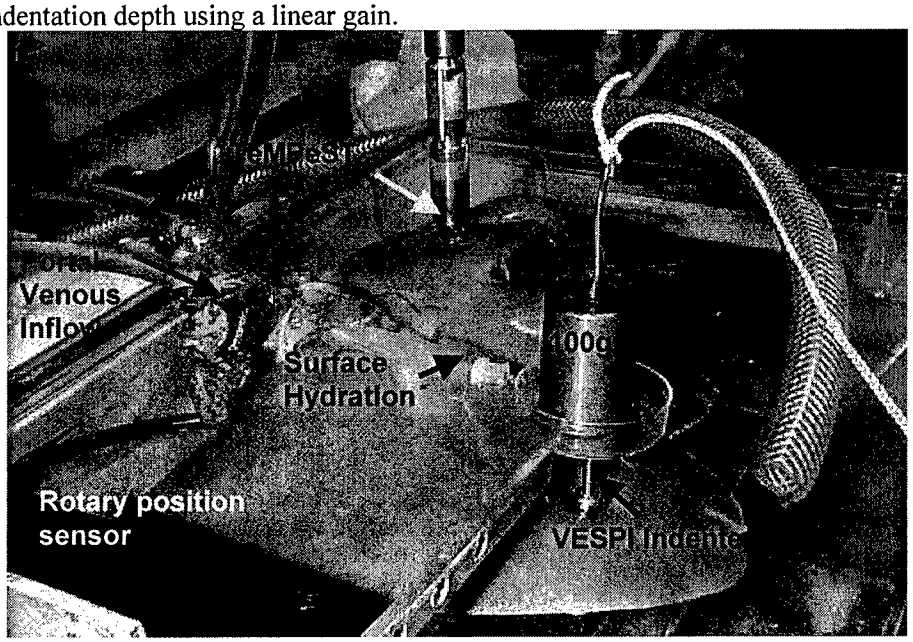

Figure 2: The TeMPeST and the VESPI devices testing 2 separate locations on the same pig liver maintained in the normothermic extracorporeal perfusion system.

3.3 Test Protocol

In vivo tests were performed on deeply anesthetized animals on assisted ventilation with 100% oxygen. The TeMPeST instrument was used to acquire compliance data on either one or two locations on the liver during data acquisition periods of approximately 20 seconds. During this time, ventilation was suspended to prevent pulmonary motions from saturating the position sensor measurements. Indentations using the VESPI device were made at the same location(s), but without the necessity for suspending ventilation. Organ thickness measurements were taken prior to every VESPI measurement with a 0-25mm dial indicator. Initial position senor values were noted and loads were applied for 300 seconds. Once the load was removed the organ was allowed to recover to its preindented state (typically 200s, as was determined by comparing the rotary position sensor to the preloaded value).

Following *in vivo* testing, heparin was injected systemically to prevent clotting, and the animal was sacrificed. The liver was harvested, and a lobe was removed and tested immediately with the TeMPeST (*in vitro* testing). The cut surface of the reminder of the organ was cauterized to prevent leakage and the organ was flushed with heparinized lactated Ringer's solution, packed in ice and transported to the laboratory.

Upon arrival (60 – 80min post-sacrifice), the liver was connected to the arterial and hepatic venous perfusate reservoirs, and allowed to come to physiological temperature before testing was resumed. TeMPeST and VESPI tests were performed in the same locations as the *in vivo* tests to minimize variation in the measurements due to the unknown locations of large vessels or connective tissues within the organ. Testing on the excised (untreated) lobe were also performed over time with both instruments. Times of sacrifice, and initiation and termination of perfusion were recorded to permit examination of measurements over time.

Following the completion of testing on the perfused organ (typically 2 hours), perfusate flow was stopped, and the organ was tested again over time to observe any further changes in the response (typically 1 hour).

The research was conducted in compliance with the Animal Welfare Act Regulations and other Federal statutes relating to animals and experiments involving animals and adheres to the principles set forth in the Guide for Care and Use of Laboratory Animals, National Research Council, 1996.

4. Results

Variations in the measured responses are observed between all of the conditions under consideration, including both changes in the measured tissue stiffness and the time dependent viscous character of the responses. The measurements performed with the TeMPeST and VESPI will be shown in the following sections.

4.1 TeMPeST Results

Figure 3 shows the frequency response calculated from ratio of the FFTs of the position and force signals, together with the ideal first order filter response of a Voigt tissue model. As the response appears to have a –20dB/decade slope after the break, and the phase lag at high frequencies is approximately –90°, the Voigt/first order response is a reasonable first approximation to fit the results. It is observed that the *in vivo* measurements show the highest compliance (lowest stiffness), while the perfused tissues are stiffer, and the unperfused tissues (after prior perfusion) are the stiffest. In addition, the break of the response shifts to higher frequencies in each of these cases.

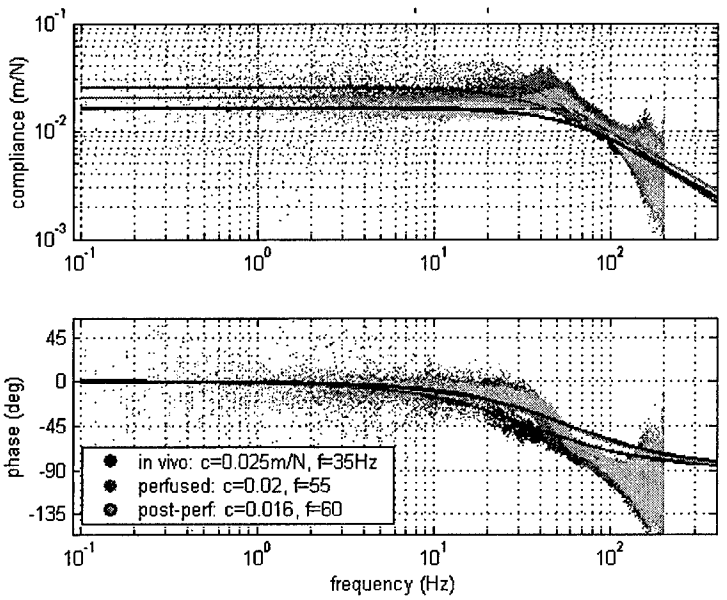

Figure 3: Frequency response of tissue measured with TeMPeST and Voigt model approximation of tissue response. First order filter characteristics include asymptotes to better show characteristic frequency (dashed lines).

4.2 VESPI Results

Figure 4 shows representative results for three conditions made on the same liver taken at the same location. Strain is calculated as depth of indentation normalized with respect to thickness measured prior to that specific test. It can be seen that the tissue *in vivo* is softer than perfused tissue, which in turn is softer than the unperfused organ. Not shown is the data from the *in vitro* experiment, which was much softer than all other conditions and which never fully achieved a steady strain state. Most significantly, the perfused steady state strain is within 17% of the *in vivo* value, much closer than the unperfused strain, which differs by more than 50% (considering 3rd indentation for each case).

We were also interested in examining the repeatability of the measurements within location. Figure 4 also shows that after allowing the tissue to recover fully after testing, the *in vivo* time responses are very similar to each other, as are the perfused tests. The unperfused test, because an external source of perfusate is no longer available, does not recover, and significant changes are observed between the first and third measurements.

Lastly, the curvature of the results provide insight to the creep time constants in the tissue. A quantitative analysis of the results will need to be performed, but qualitatively it can be seen that the curves of the various conditions are indeed different suggesting that the testing conditions alter the viscous properties of the tissue.

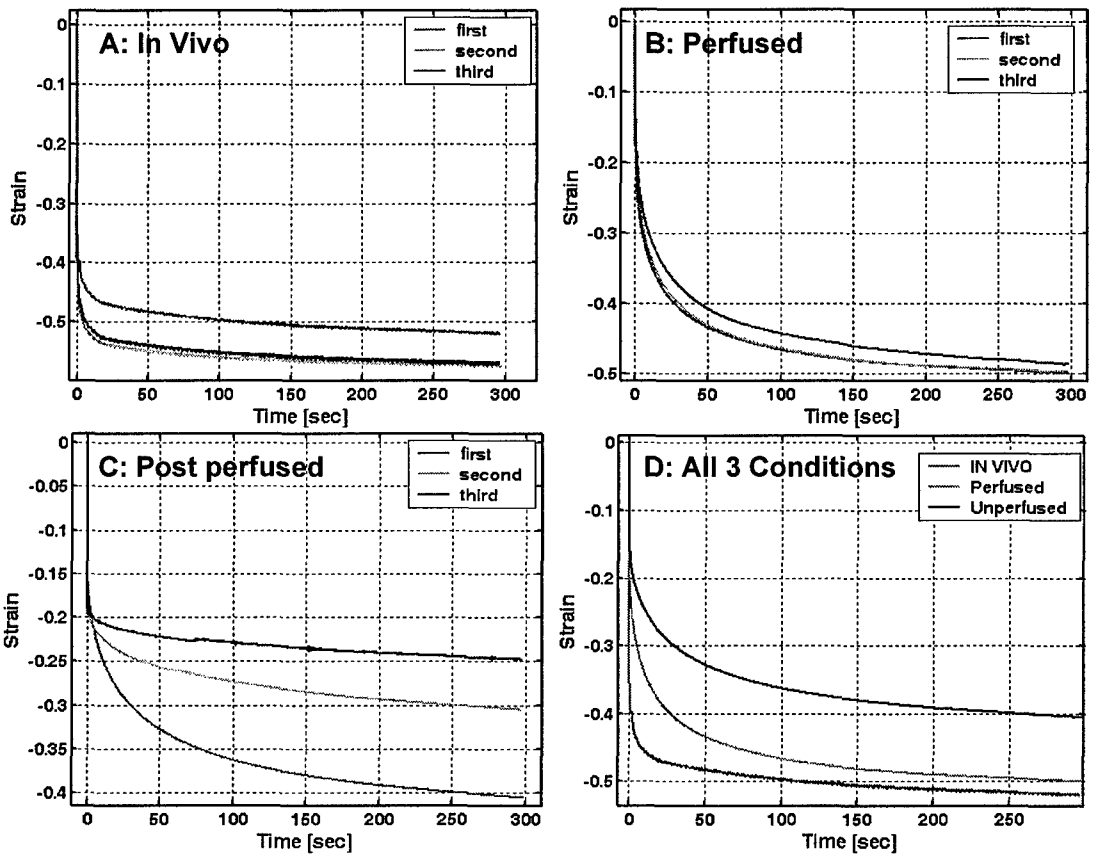

Figure 4: VESPI response for all four conditions under consideration on a 27kg pig liver at the same location. (A) In vivo 100g load. The second and third indentations were taken 10 and 50 minutes after the first. (B) Perfused 100g load. The second and third indentations were taken 20 and 48 minutes after the first. (C) Unperfused 100g load. The first indentation was taken 1 minute post perfusion while the second and third were 12 and 25 minutes after that (D) Results of the first indentation performed at each condition.

5. Conclusions and Future Work

Humans can feel differences in force as small as 10% [17]. For this reason, employing measurements from unperfused tissue as a proxy for perfused (or *in vivo*) data may result in significant inaccuracies in surgical simulators for training. For example, if one becomes accustomed to manipulating virtual tissues that are stiffer than real ones, excessive, possibly damaging forces may be applied when the trainee reaches the operating room. We hypothesized that in creating an environment that closely approximates *in vivo* conditions, we can maintain the mechanical viability of the tissue such that the

properties we measure *ex vivo* are comparable to the *in vivo* properties and that without such an environment, the material properties are altered beyond 10%.

Each of the instruments shows variations in the stiffness and damping properties of the liver depending on the test condition. However, the large deformation time responses, when using the perfusion apparatus, approach those of tissues tested *in vivo*. The flow of perfusate permits the organ to fully recover after testing, just as the flow of blood through the living organ would. In addition the static pressure applied to the perfusate provides an internal "boundary condition" to the tissue which is present (at least on average) in the living organ, but is absent when testing tissues on the lab bench, even if immersed in physiological solution.

The TeMPeST measurements show the high frequency response of the tissue, showing a slight increase in the break frequency after the tissues have been perfused. One possible explanation is that the Lactated Ringer's solution, mostly water, behaves as a Newtonian fluid, with a viscosity lower than that of the non-Newtonian blood that normally perfuses the tissues. Whether this is a noticeable error from the perspective of simulation is a question that cannot be answered in this study, however if diagnostic applications are envisioned, it may be necessary to refine the perfusion system further to ensure a closer match in behavior over a wide range of time scales.

More recent examination of the literature has shown that the perfusion pressure for the hepatic portal branch of the system is currently too high. In particular, the 20mmHg value is more than double the published value of 9mmHg [18]. Measurements of *in vivo* portal venous and arterial pressure will be performed in future experiments and the static pressures of the system will be altered accordingly.

Tests scheduled, but not yet performed include testing whole organs over time in both the untreated case and in the flushed-unperfused case.

In conclusion, it was confirmed that untreated tissues behave much differently than tissues *in vivo*, and that the perfusion system provides a suitable environment for testing whole organ tissues. The maintenance of hydration, temperature, osmotic balance and internal pressure are necessary to permit extended testing of whole organs on the lab bench, where testing can be conducted more conveniently than in the operating room. In addition, the perfusion system will enable the use of organs harvested from other sources, without ever performing dedicated *in vivo* tests, reducing the cost of testing and the ethical and administrative issues of *in vivo* testing. It is recommended that researchers performing soft tissue testing on solid organs make use of similar systems to provide mechanical function support to tissues tested in the laboratory setting.

6. Acknowledgements

Support for this work has been provided by a grant from the US Army, under contract number DAMD 17-01-1-0677. The ideas and opinions presented in this paper represent the views of the authors and do not, necessarily, represent the views of the Department of Defense.

7. References

[1] P.S. Wellman. Tactile Imaging. Ph.D. Thesis, Division of Engineering and Applied Sciences, Harvard University, Cambridge (1999) p137.

[2] T. A. Krouskop, T. M. Wheeler, F. Kallel, B. S. Garra, T. Hall. Elastic Moduli of Breast and Prostate Tissues Under Compression. *Ultrasonic Imaging*, **20** (1998) pp260-274.

[3] I. Brouwer, J. Ustin, L. Bentley, A. Sherman, N. Dhruv, F. Tendick. Measuring In Vivo Animal Soft Tissue Properties for Haptic Modeling in Surgical Simulation. Proc. Medicine Meets Virtual Reality 2001, Newport Beach, CA. IOS Press. pp69-74.

[4] J. Kim, B.K. Tay, N. Stylopoulos, D.W. Rattner, M.A. Srinivasan. Characterization of Intra-abdominal Tissues from In Vivo Animal Experiments for Surgical Simulation. Proc. Medical Image Computing & Computer Assisted Intervention (MICCAI), Montreal, Canada, (2003) pp206-213.

[5] F.J. Carter, T.G. Frank, P.J. Davies, D. McLean, A. Cuschieri. Measurements and modelling of the compliance of human and porcine organs. *Medical Image Analysis*, **5**(4) (2001) pp231-6.

[6] M.P. Ottensmeyer. In vivo measurement of solid organ visco-elastic properties. Proc. Medicine Meets Virtual Reality 02/10 (MMVR02/10), Newport Beach, CA. IOS Press. (2002) pp328-33.

[7] J. D. Brown, J. Rosen, Y. S. Kim, L. Chang, M. Sinanan, B. Hannaford. In-Vivo and In-Situ Compressive Properties of Porcine Abdominal Soft Tissues. Proc. Medicine Meets Virtual Reality 11, Newport Beach, CA. IOS Press. (2003) pp26-32.

[8] K. Miller, K. Chinzei, G. Orssengo, P. Bednarz. Mechanical properties of brain tissue in-vivo: experiment and computer simulation. *J. Biomechanics*, **33** (2000) pp1369-1376.

[9] K. Miller. Biomechanics of Soft Tissues. *Medical Science Monitor*, **6** (2000) pp158-167.

[10] M. Farshad, M. Barbezat, P. Flueler, F. Schmidlin, P. Graber, P. Niederer. Material Characterization of the Pig Kidney in Relation with the Biomechanical Analysis of Renal Trauma. *Journal of Biomechanics*, **32** (1999) pp417-425.

[11] M. Kauer, V. Vuskovic, J. Dual, G. Szekely, M. Bajka. Inverse Finite Element Characterization of Soft Tissues. Proc. Medical Image Computing and Computer-Assisted Intervention, (MICCAI) Utrecht, Netherlands (2001) 128-136.

[12] T. Hu, J. Desai. A Biomechanical Model of the Liver for Reality-Based Haptic Feedback. Proc. Medical Image Computing & Computer Assisted Intervention (MICCAI), Montreal, Canada, (2003) pp75-82.

[13] Y. C. Fung, *Biomechanics: Mechanical Properties of Living Tissues*, second ed. New York: Springer-Verlag, 1993.

[14] M. Schon, O. Kollmar, S. Wolf, H. Schrem, M. Matthes, N. Akkoc, N. Schnoy, P. Neuhaus. Liver Transplantation After Organ Preservation with Normothermic Extracorporeal Perfusion. *Annals of Surgery*, **233** (2001) pp114-123.

[15] K. P. Platz, A. R. Mueller, C. Schafer, S. Jahns, O. Guckelberger, P. Nehaus. Influence of Warm Ischemia Time on Graft Function in Human Liver Transplantation. *Transplantation Proceedings*, **29** (1997) pp3458-3459.

[16] C. Bruyns, M.P. Ottensmeyer. Measurements of Soft-Tissue Mechanical Properties to Support Development of a Physically Based Vrtual Animal Model. Proc. Medical Image Computing and Computer-Assisted Intervention, MICCAI 2002, Tokyo, Japan (25-28 Sept 2002) pp282-289

[17] S. Allin, Y. Matsuoka, R. Klatzky. Measuring Just Noticeable Differences for Haptic Force Feedback: Implications for Rehabilitation. Proc. 10th Symposium On Haptic Interfaces for Virtual Environments & Teleoperator Systems (HAPTICS '02), Los Alamitos, CA, IEEE. pp299-302.

[18] A. Rasmussen, C. Skak, M. Kristensen, P. Ott, P. Kirkegaard, N.H. Secher. Preserved arterial flow secures hepatic oxygenation during haemorrhage in the pig. *Journal of Physiology*, **516**(2) (1999) pp539-548.

A Nonlinear Finite Element Model of Soft Tissue Indentation

Yi Liu[1], Amy E. Kerdok[1,2], Robert D. Howe[1, 2]

[1] Harvard University Division of Engineering and Applied Sciences
[2] Harvard/MIT Division of Health Sciences and Technology
kerdok@fas.harvard.edu

Abstract. Mathematically describing the mechanical behavior of soft tissues under large deformations is of paramount interest to the medical simulation community. Most of the data available in the literature apply small strains (<10%) to the tissue of interest to assume a linearly elastic behavior. This paper applies a nonlinear hyperelastic 8-chain network constitutive law to model soft tissues undergoing large indentations. The model requires 2 material parameters (initial modulus, locking stretch) to reflect the underlying physics of deformation over a wide range of stretches. A finite element model of soft tissue indentation was developed and validated employing this constitutive law. Ranges of the initial shear modulus and locking stretches were explored based on values found for breast tissue [17, 25]. Results of the model are shown with a lookup table containing third order polynomial coefficient fits. This work serves as an initial method to determine the unique material parameters of breast tissue from indentation experiments.

1. Introduction

Accurate mathematical descriptions of the mechanical behavior of soft tissues remain the limiting factor in the advancement of realistic medical simulations and non-invasive diagnostic tools. This is due to the complex nonlinear material properties of soft tissues when they undergo large mechanical deformations during minimally invasive procedures and diagnostic palpations.

A phenomenological approach is implemented to realize the material parameters of soft tissues. Inverse finite element modeling (FEM) is used to fit mathematical expressions in the form of a constitutive law to experimental data. Soft tissues are most often tested in an *ex-vivo* state with specimens of finite thickness under controlled loading and boundary conditions [8, 15, 18]. Selecting the appropriate constitutive law allows FEM to then be used to predict the tissue's response to modes of deformation not capable of being experimentally measured. We are interested in modeling the indentation of soft tissues by a rigid flat-ended cylindrical punch.

This paper provides a method for determining an initial estimate of the material parameters of soft tissue using the Arruda-Boyce constitutive model. A range of the two physically based material parameters of this model were explored based on data found in the literature on normal and pathologic breast tissue [17, 21, 22, 25]. The resulting force-nominal strain plots were fitted to 3rd order polynomials whose

coefficients and the resulting material parameters are presented. Others have attempted to model breast tissue under uniaxial compression and assumed linear elasticity [3, 20]. Han assumed quasilinear viscoelasticity with an exponential elastic response and modeled the breast under plain strain conditions because he used a rectangular shaped probe on thick specimens [10].

Results indicated here should serve as a means for identifying an estimate of the physiologically based material parameters of the Arruda-Boyce model.

2. Background

There exists a well-defined analytic solution for indentation by a rigid flat punch assuming infinitesimal strains, frictionless contact, and a semi-infinite incompressible elastic half-space [14, 24]. To account for the finite thickness in indentation experiments on cartilage, Hayes expanded the analytical solution to include a term that is dependant on the sample thickness:

$$P = \frac{2aEw}{(1-\nu^2)}\kappa\left(\frac{a}{h},\frac{w}{h}\right) \tag{1}$$

where P is the applied force, E is the elastic modulus, a is the radius of the indenter, w is the depth of indentation, and κ is a dimensionless term to account for sample thickness (Fig. 1) [11]. Zheng created a finite element model using equation (1) to explore the effects of nonlinear geometry, namely large deformations up to 15% nominal strain, compressibility, and friction on the indentation of cartilage attached to a semi-infinite rigid half space [28]. Our goal is to further this approach by introducing both larger strains (~50%), and material nonlinearities into a FEM of soft tissue under indentation.

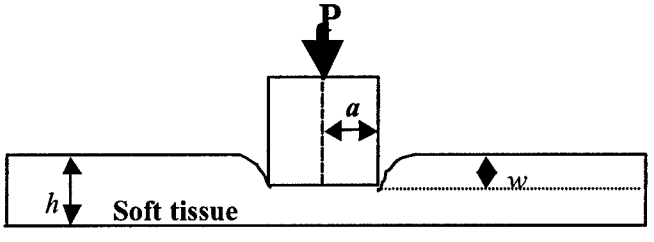

Fig. 1. Conceptual diagram of the soft tissue indentation model.

It is well understood that soft tissues are viscoelastic, anisotropic, inhomogeneous, and have nonlinear force displacement characteristics [9]. To simplify the mathematical analysis, many researchers assume an initial isotropy, local homogeneity, and study tissue deformations in the linear regime of <10% nominal strain [17, 19, 25]. However, typical surgical manipulations are often much larger than 10% nominal strain. It has been shown that at larger strains an elastic contrast

exists between tissues of different pathologic states [17, 25, 27]. Therefore more accurate representations of soft tissue behavior are needed.

Holzapfel suggests that only biological materials and solid polymers (rubber-like materials) undergo finite strains elative to an equilibrium state [12]. Therefore it should not be surprising that the hyperelastic constitutive models developed for elastomers have frequently been used to study soft tissues [5, 8, 9, 13, 15, 16, 18, 23]. Hyperelastic materials are considered initially isotropic and exhibit a nonlinear instantaneous response up to large strains. There are two ways in which the strain energy functions for hyperelastic materials are derived: one based on continuum mechanics and the other based on statis tical mechanics.

We have created a FEM with a hyperelastic constitutive model based on statistical mechanics. We describe that model and the predictions it makes for large strain indentations of pathologic breast tissues.

3. Materials and Methods

3.1 Creating and Validating the Finite Element Model

Using commercial finite-element software (ABAQUS 6.3-1, HKS, Rhode Island), the present investigation created an axisymmetric rigid indenter model to analyze the indentation of soft tissue (Fig. 2). The model was validated against the analytical solution presented in equation 1 (with both $\kappa=1.0$ and $\kappa>1.0$) and compared to Zheng et al's [28] finite element model under infinitesimal strains before adding a nonlinear constitutive law.

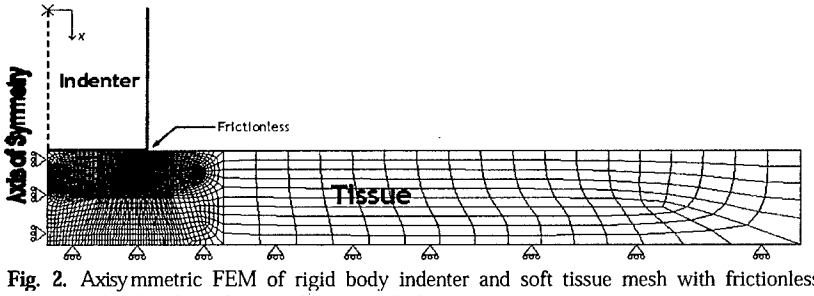

Fig. 2. Axisymmetric FEM of rigid body indenter and soft tissue mesh with frictionless contact and sliding boundary conditions on the base.

The indenter was modeled as an analytical rigid body with a flat-ended cylindrical shape 12mm in diameter. Initially the tissue (cartilage) was modeled as a deformable meshed layer and was assumed to be linearly elastic, isotropic, and incompressible with Young's modulus E=100 kPa and Poisson's ratio v=0.4999[1] [28]. Its mesh consisted of 4-noded hybrid quadrilateral axisymmetric elements (CAX4H), finely biased in the immediate regions underneath the indenter as shown in Figure. 2. The

[1] Due to ABAQUS' limitations when v=0.5, an incompressibility of v=0.4999 was used.

contact between the indenter and the tissue was modeled using a "contact pair" where the indenter was specified as "master" and the tissue as "slave." The contact property was defined as frictionless so that the tissue could freely slip beneath the indenter. Known displacements were then applied to the reference node of the indenter that was initially oriented on the surface of the tissue. The reaction forces generated by the FE simulation were recorded and plotted against strain.

To validate the model against the case of the true analytical solution of a rigid flat punch (equation 1 where κ=1.0), the boundary condition of the bottom surface is free. The tissue was unconstrained in the lateral direction and an aspect ratio (indenter radius to sample thickness) of 0.1 was used to approximate the semi-infinite elastic half space. Results from the FEM under 0.1% nominal strain are within 3.3% of the analytical form of the solution.

The FEM was modified to validate against Hayes' analytical model (κ>1.0 in equation 1). Fixed boundary conditions simulated the attachment of cartilage to a rigid bony layer [11]. Two aspect ratios were tested (0.2 and 1.0) to a strain of 0.1%. Less than 2% error occurs when the FEM accounts for finite tissue thickness and is compared to both Hayes' analytical solution and Zhang's FEM results at nominal strains of 0.1% (Table 1).

Table 1. A comparison of the kappa value between our model (Liu) and the analytical solution of Hayes and the FEM of Zheng for 2 different aspect ratios.

Aspect ratio	Model	κ	% Error
a/h = 0.2	Liu	1.260	-
	Zhang	1.244	1.25
	Hayes	1.281	-1.67
a/h = 1.0	Liu	3.564	-
	Zhang	3.590	-0.72
	Hayes	3.609	-1.24

After the model was validated assuming linear elasticity under infinitesimal strains, the model was changed to simulate soft tissue indentation tests containing both geometric and material property nonlinearities. Experiments on breast tissue indentation found in the literature allow for frictionless contact between both the indenter and the specimen, and between the specimen and the testing surface [17, 25]. Thus, the boundary condition on the bottom surface of the tissue in the model was unconstrained in the lateral direction. To compare to the experimental breast tissue data, the indenter size was changed to 4mm in diameter and aspect ratios of 0.5, 1.0, and 1.5 were created [17, 25]. The indenter fillet was increased to $2x10^{-4}$ mm to allow the tissue to be compressed to 50% nominal strain The mesh bias was refined until a model of each aspect ratio could reach the set strain of 50%. Strain rate tests performed on breast tissue suggest that viscous effects can be neglected [17, 25]. Hyperelastic nonlinear material parameters were added to the material property definitions of the tissue in the indentation model. Specifically, the Arruda-Boyce constitutive law was selected.

3.2 The Arruda-Boyce Constitutive Model

3.2.1 Motivation

The continuum mechanics approach for developing hyperelastic strain energy functions are empirical, need more than one experiment to realize their many material parameters, and have a limited strain region over which their results are applicable. Although higher order models fit the data well, they are complex, computationally expensive, and unstable at high stretches [1, 4]. Despite these difficulties they are still widely used to describe the behavior of soft tissues [5, 8, 9, 13, 15, 16, 18, 23].

The statistical mechanics treatment of rubber elasticity (Langevin chain statistics) model the material chain segment between chemical cross-links as a rigid link with set length [4]. The stress-strain behavior is governed by changes in configurational entropy [2]. The end result reflects the underlying physics of macroscopic deformation from microscopic components. In particular the Arruda-Boyce model is an 8-chain network model where only two material parameters (the rubbery initial modulus and the limiting chain extensibility) are needed to describe the behavior of a material over a wide range of stretches given limited test data. This model lends itself ideally to that of soft tissues because the polymer chains mimic their main constituents: collagen and elastin fibers.

3.2.2 Development

A convenient form of the Arruda-Boyce strain energy function, U, is found by taking a series expansion of the inverse Langevin function to the 5th order:

$$U = \mu \sum_{i=1}^{5} \frac{C_i}{\lambda_m^{2i-2}} \left(\overline{I_1^i} - 3^i \right) + \frac{1}{D} \left(\frac{J_{el}^2 - 1}{2} - \ln J_{el} \right) \tag{2}$$

where

$$C_1 = \frac{1}{2}, C_2 = \frac{1}{20}, C_3 = \frac{11}{1050}, C_4 = \frac{19}{7000}, C_5 = \frac{519}{673750} \tag{3-7}$$

$$\mu = nK\theta \tag{8-10}$$
$$\lambda_m = \sqrt{N}$$
$$\overline{I_1} = tr(\lambda) = \lambda_1^2 + \lambda_2^2 + \lambda_3^2.$$

Here μ is the initial rubbery shear modulus, n is the chain density, θ is the temperature, K is Boltzmann's constant, λ_m is the limiting chain extensibility (locking stretch), N is the number of rigid links, I_1 is the first deviatoric strain invariant, and λ_i are the principle stretches. D is a temperature dependant material parameter related to the bulk modulus, and J_{el} is the elastic volume ratio. For incompressible materials, $J_{el} = 1$ and the second term in equation 2 drops out.

Due to symmetry each chain's stretch is shared equally amongst all of the chains and an initially isotropic configuration can be assumed. We can therefore relate the microscopic chain length to the macroscopic principal stretches via:

$$\lambda_{chain} = \frac{1}{\sqrt{3}}\left(\sqrt{\lambda_1^2 + \lambda_2^2 + \lambda_3^2}\right) = \frac{l}{l_0} \tag{11}$$

where λ_{chain} is the chain stretch, l is the current chain length, and l_0 is the initial chain length. The locking stretch, λ_m, is the value of the chain stretch when t reaches its fully extended state, and can be determined from a simple tension or compression experiment assuming incompressibility ($\lambda_1\lambda_2\lambda_3=1$). Modeling a uniaxial compression state and noting from the literature that breast tissue drastically increases its stress response at strains on the order of 30% nominal strain for normal tissue and 10% nominal strain for cancerous tissue, locking stretches were calculated to be 1.05 and 1.01 respectively.

Literature on breast tissue material property measurements of varying pathology suggest that initial elastic moduli for cancerous tissue is between 3 and 7 times that of normal tissue [17, 21, 22, 25]. For an incompressible material Possion's ratio is 0.5 and the elastic modulus is equal to 3 times the shear modulus. Given initial elastic moduli reported in the literature of 33 kPa and 100-186 kPa for normal and infiltrating ductal carcinoma respectively at 5% nominal strain, we explored initial shear moduli between 1 kPa and 150 kPa.

3.3 Applying the nonlinear constitutive law to the FEM

Using the proposed FE model, we chose to model eight different combinations of the two material parameters of the Arruda-Boyce constitutive law over three different aspect ratios (a/h = 0.5, 1.0, 1.5): μ=1, 5, 10, 20 kPa with λ_m = 1.05, and μ=30, 60, 100, 150 kPa with λ_m = 1.01. The models were deformed to 50% nominal strain and the displacement and reaction force in the axis of deformation were recorded.

The Arruda-Boyce model is typically used for very large strains (i.e. tensile strains > 200%). We are only interested in compressive strains on the order of 50%. We can assume the effects from the higher order polynomial terms are therefore negligible. Third order polynomials were fit to the force-nominal strain curves generated from our FEM analysis. The coefficients of these polynomials can be compared to experimental data to estimate the material parameters of the substrate under study.

4. Results

The force-nominal strain responses of the FEM with different values of the initial shear modulus and locking stretch material parameters of the Arruda-Boyce constitutive model are shown below in Figure 4. Eight values of the initial modulus ranging from 1 kPa to 150 kPa were modeled with two values of the locking stretch (1.01 and 1.05) based on breast tissue data found in the literature as previously stated. Three aspect ratios were modeled to account for different sample thickness and indenter geometry. Typical computation times for 50% strain on a Pentium III computer were on the order of 140 seconds. The coefficients of third order polynomials fit to the model's response and their R^2 values are shown in Table 2.

Table 2. The material parameters of the Arruda-Boyce model and their resulting third order polynomial fit coefficients for the force-nominal strain responses of soft tissue indentation.

a/h = 0.5

R^2	A	B	C	lambda	mu (kPa)
0.9997	1.48	0.53	0.31	1.05	1
0.9997	7.46	2.72	1.56	1.05	5
0.9997	14.80	5.28	3.11	1.05	10
0.9997	29.88	10.83	6.25	1.05	20
0.9997	57.43	20.83	10.90	1.01	30
0.9997	113.81	41.21	21.69	1.01	60
0.9997	187.01	67.21	35.87	1.01	100
0.9996	275.91	98.22	53.38	1.01	150

a/h = 1.0

R^2	A	B	C	lambda	mu (kPa)
0.9995	1.20	0.43	0.23	1.05	1
0.9995	5.92	2.10	1.16	1.05	5
0.9995	11.73	4.16	2.30	1.05	10
0.9995	23.16	8.17	4.58	1.05	20
0.9995	43.93	15.43	7.93	1.01	30
0.9995	86.04	29.99	15.71	1.01	60
0.9995	140.78	48.72	25.93	1.01	100
0.9995	207.65	71.35	38.55	1.01	150

a/h = 1.5

R^2	A	B	C	lambda	mu (kPa)
0.9995	1.19	0.44	0.22	1.05	1
0.9995	5.85	2.17	1.07	1.05	5
0.9995	11.56	4.27	2.13	1.05	10
0.9995	22.75	8.38	4.22	1.05	20
0.9994	42.98	15.75	7.31	1.01	30
0.9994	83.87	30.52	14.44	1.01	60
0.9994	136.84	49.49	23.79	1.01	100
0.9994	201.47	72.42	35.31	1.01	150

5. Conclusions and Future Work

For realistic medical simulations to become a practical reality the acquisition of biomechanical information and efficient computation must be achieved. The latter is left to the many researchers working on deformable meshing techniques [6, 7, 26]. It was the intent of this paper to focus on uniquely characterizing the complex nonlinear behavior of soft tissues with a simple mathematical model given limited experimental data. We implemented such a model in finite element simulations to predict the behavior of soft tissues undergoing large indentation deformations across various testing geometries. The model was validated in the linear regime against analytical solutions and another FEM. The force-nominal strain results of the model can be used to estimate the material parameters of the soft tissue of interest.

An axisymmetric finite element model with frictionless contact and boundary conditions was created employing the hyperelastic Arruda-Boyce constitutive model. Unlike similar constitutive laws formulated from continuum mechanics, this statistcal mechanics based model was chosen because its two material parameters have a physical interpretation that can be directly related to the constituent make-up of soft tissues (collagen and elastin fibers).

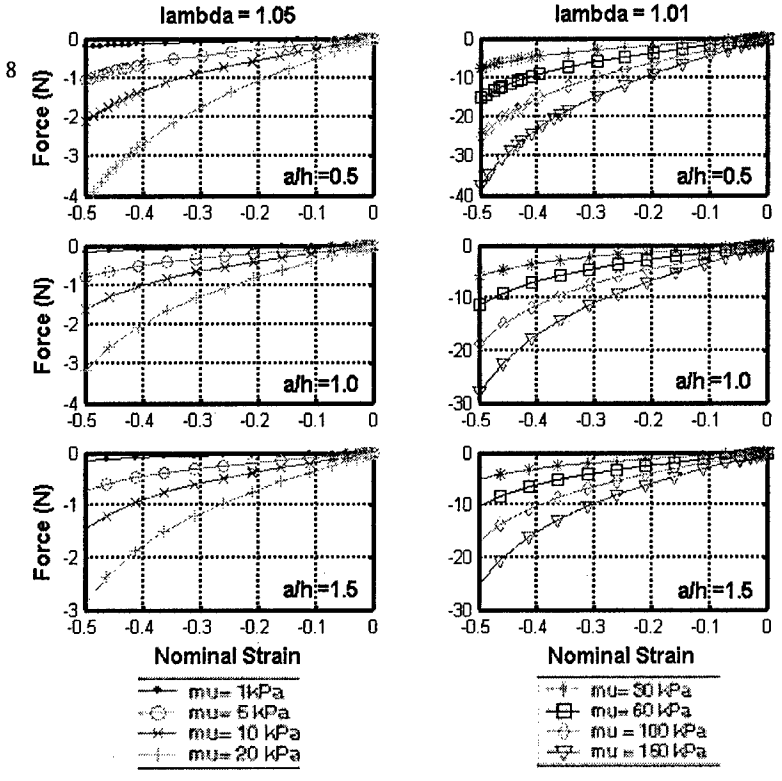

Fig. 4. Force versus nominal strain results for the FEM with a/h=0.5 (top), a/h=1.0 (middle), and a/h=1.5 (bottom) across various initial shear moduli and locking stretches (λ_m =1.05 (left) and (λ_m =1.01 (right)) up to 50% nominal strain.

Most of the soft tissue data published in the literature only apply nominal strains of up to 10%. At these low strains, the Arruda-Boyce model reduces to the linear elastic Neo-Hookean form and fits the data well. At strains where the usefulness of these elastic models is of limited value the Arruda-Boyce model continues to predict the nonlinear behavior of the soft tissues.

Wellman has collected some indentation data on pathologic breast samples at larger strains (>35% nominal strain). A future study will analyze this data and compare it to nonlinear FEM simulations to determine the unique material properties of the tissue. The lookup tables presented in this paper will be used to obtain approximate initial values for the material parameters. An iterative process will then ensue where the models' results will be compared to the large strain data via the employment a nonlinear search scheme minimizing the sum of squares error. With an educated estimate of the initial value of the material parameters, convergence of a unique set of material parameters can be quickly obtained to within the standard error of the data collected.

A preliminary set of both normal glandular and cancerous data are plotted together with the corresponding FEM results in Figure 5. Fitting a third order polynomial to the data in Figure 5 suggests that an estimate for the normal glandular tissue material parameters are on the order of λ_m=1.05 and μ=1 kPa (a/h=1.0) and for infiltrating ductile carcinoma λ_m=1.01 and μ=30 kPa (a/h=1.5).

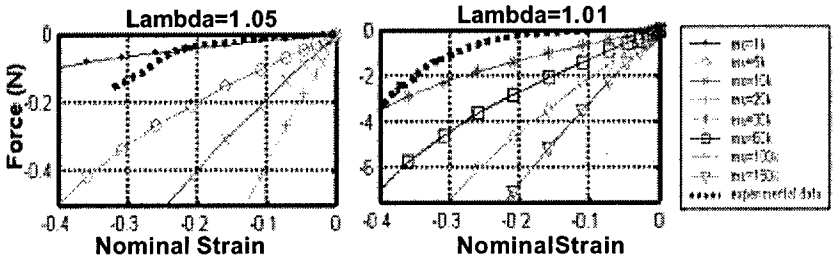

Fig. 5. Preliminary large strain indentation data plotted for normal breast tissue with a/h=1.0 (left) and infiltrating ductile carcinoma (right) against FEM results with a/h=1.5.

It is clear from this preliminary work that the model needs further development. The tissue appears to have a lower locking stretch than the Arruda-Boyce model predicts. This is most likely because the Arruda-Boyce model assumes an initial stress-free reference state, where as in real tissue this does not exist due to hydration and tension in the fibers. Accounting for this non-zero initial stress state should bring the model into closer agreement with the data and is currently being developed.

6. References

1. Anand, L.: A Constitutive Model for Compressible Elastomeric Solids. Computational Mechanics, 18. (1996) 339-355
2. Arruda, E.M.Boyce, M.C.: A Three-Dimensional Constitutive Model for The Large Stretch Behavior of Rubber Elastic Materials. J. Mech. Phys. Solids, 41. (1993) 389-412
3. Azar, F.S., Metaxas, D.N.Schnall, M.D.: A Deformable Finite Element Model of the Breast for Predicting Mechanical Deformations under External Perturbations. Journal of Academic Radiology, 8. (2001) 965-975
4. Boyce, M.C.Arruda, E.M.: Constitutive Models of Rubber Elasticity: A Review. Rubber Chemistry and Technology, 73. (2000) 504-523
5. Carter, F.J., Frank, T.G., Davies, P.J., McLean, D.Cuschieri, A.: Measurements and Modeling of the Compliance of Human and Porcine Organs. Medical Image Analysis, 5. (2001) 231-236
6. Cotin, S., Delingette, H.Ayache, N.: Real-Time Elastic Deformations of Soft Tissues for Surgery Simulation. IEEE Transactions on Visualization and Computer Graphics, 5. (1999) 62-73
7. Delingette, H.: Towards Realistic Soft Tissue Modeling in Medical Simulation. In: IEEE: Special Issue in on Virtual and Augmented Reality in Medicine, 86. 1998) 12
8. Farshad, M., Barbezat, M., Flueler, P., Schmidlin, F., Graber, P.Niederer, P.: Material Characterization of the Pig Kidney in Relation with the Biomechanical Analysis of Renal Trauma. Journal of Biomechanics, 32. (1999) 417-425
9. Fung, Y.C.: Biomechanics: Mechanical Properties of Living Tissues. second. Springer-Verlag, New York (1993)
10. Han, L., Noble, J.A.Purcher, M.: A Novel Ultrasound Indentation System for Measuring Biomechanical Properties of in Vivo Soft Tissue. Ultrasound in Medicine & Biology, 29. (2003) 813-823

11. Hayes, W.C., Keer, L.M., Hermann, G.Mockros, L.F.: A Mathematical Analysis for Indentation Tests of Articular Cartilage. J. Biomechanics, 5. (1972) 541-551
12. Holzapfel, G.A.: Nonlinear Solid Mechanics: A Continuum Approach for Engineering. John Wiley & Sons Ltd., West Sussex, England (2000)
13. Hutter, R., Schmitt, K.-U.Niederer, P.: Mechanical Modeling of Soft Biological Tissues for Application in Virtual Reality Based Laparoscopy Simulators. Technology and Health Care, 8. (2000) 15-24
14. Johnson, K.L.: Contact Mechanics. Cambridge University Press, Cambridge, UK (1985)
15. Kauer, M., V. Vuskovic, J. Dual, G. SzekelyM. Bajka: Inverse Finite Element Characterization of Soft Tissues. In: Medical Image Computing and Computer-Assisted Intervention - MICCAI. (Utrecht, The Netherlands, 2001) 128-136
16. Kim, J., Tay, B., Stylopoulos, N., Rattner, D.W.Srinivasan, M.A.: Characterization of Intra-Abdominal Tissues from in Vivo Animal Experiment for Surgical Simulation. In: MICCAI. 2003)
17. Krouskop, T.A., Wheeler, T.M., Kallel, F., Garra, B.S.Hall, T.: Elastic Moduli of Breast and Prostate Tissues under Compression. Ultrasonic Imaging, 20. (1998) 260-274
18. Miller, K.: Biomechanics of Soft Tissues. Med. Sci. Monit, 6. (2000) 158-167
19. Ottensmeyer, M.P.: *In Vivo* Data Acquisition Instrument for Solid Organ Mechanical Property Measurement. In: Medical Image Computing and Computer-Assisted Intervention - MICCAI. (Utrecht, The Netherlands, 2001) 975-982
20. Plewes, D.B., Bishop, J., Samani, A.Sciarretta, J.: Visualization and Quantization of Breast Cancer Biomechanical Properties with Magnetic Resonance Elastography. Physics in Medicine and Biology, 45. (2000) 1591-1610
21. Sarvazyan, A.P., Skovoroda, A.R.Pyt'ev, Y.P.: Mechanical Introscopy - a New Modality of Medical Imaging for Detection of Breast and Prostate Cancer. In: Eighth IEEE Symposium on Computer Based Medical Systems. 1997)
22. Skovoroda, A.R., Klishko, A.N., Gusakyan, D.A., Mayevskii, Y.I., Yermilova, V.D., Oranskaya, G.A.Sarvazyan, A.P.: Quantitative Analysis of the Mechanical Characteristics of Pathologically Changed Soft Biological Tissues. Biophysics, 40. (1995) 1359-1364
23. Szekely, G., Brechbuhler, C., Dual, J.al., e.: Virtual Reality-Based Simulation of Endoscopic Surgery. Presence, 9. (2000) 310-333
24. T imoshenko, S.Goodier, J.N.: Theory of Elasticisy. McGraw-Hill, New York (1970)
25. Wellman, P.S.: Tactile Imaging. Division of Engineering and Applied Sciences. Cambridge, Harvard University (1999) 137
26. Wu, X., Downes, M.S., Goktekin, T.Tendick, F.: Adaptive Nonlinear Finite Elements for Deformable Body Simulation Using Dynamic Progressive Meshes. In: Eurographics 2001, Computer Graphics Forum, 20. 2001) 349-358
27. Yeh, W.-C., Li, P.-C., Jeng, Y.-M., Hsu, H.-C., Kuo, P.-L., Li, M.-L., Yang, P.-M.Lee, P.H.: Elastic Modulus Measurements of Human Liver and Correlation with Pathology. Ultrasound in Medicine & Biology, 28. (2002) 467-474
28. Zhang, M., Zheng, Y.P.Mak, A.F.: Estimating the Effective Young's Modulus of Soft Tissues from Indentation Tests - Nonlinear Finite Element Analysis of Effects of Friction and Large Deformation. Med. Eng. Phys., 19. (1997) 512-517

7. Acknowledgements

The authors would like to thank Parris Wellman for the use of his data, and Prof. Simona Socrate for her assistance with the modeling.

The Effects of Testing Environment on Soft Tissue Properties

Amy Elizabeth Kerdok
Harvard University, HST-MEMP 1997

Robert D. Howe, Ph. D. Gordon McKay Professor of Engineering
Division of Engineering and Applied Sciences, Harvard University

Accurate characterization of the mechanical behavior of soft tissues is needed for medical simulation, diagnostic, and tissue engineering purposes. Determining the complex behavior of soft tissues requires mechanical testing in their natural state. Such in vivo tests are wrought with ethical, accessibility, physiological noise, and uncontrolled boundary condition issues. Several groups have developed means for in vivo mechanical testing, but the interpretation of their results remains to be understood. Conversely, testing biological tissues under ex vivo conditions is desirable because it allows for precise control of the boundary conditions, ease of accessibility, and use of fewer animals. However, the behavior and properties of the tissues are drastically altered once removed from their natural state. This study seeks to quantify the differences in the viscoelastic response of soft tissues between four different test conditions. We introduce a new ex vivo set-up that allows for near in vivo testing.

A system was developed to mimic the natural environmental condition of the liver for *ex vivo* mechanical testing. The system maintains the structural integrity of the liver post mortem by perfusing the organ with physiologic solutions at appropriate pressures and temperature (39 C). Adjusting the heights of the perfusate reservoirs kept the pressures to the hepatic artery and the portal vein at 100-120 mmHg and 15-20 mmHg respectively.

Mechanical testing was performed using the VESPI (Visco-Elastic Soft-Tissue Property Indentation) device. Large strain (>30%) indentations typical of surgical manipulations and diagnostic palpations were applied to the organ using a known load and displacements were recorded over time. These creep tests were performed on whole porcine livers *in vivo, ex vivo* perfused, and *ex vivo* unperfused on the same locations. *In vitro* tests on a sectioned lobe under warm ischemic conditions were also done. Biopsies were taken for histology on the *ex vivo* states over time and compared against an *in vivo* control.

Initial results indicate over a 50% difference in the steady state strain response of the liver between the *in vivo* and *ex vivo* unperfused states. A 17% difference is noted between the *in vivo* and the *ex vivo* perfused states. The *in vitro* condition did not achieve a steady state response within 5 minutes of load application. Both the *in vivo* and the *ex vivo* perfused conditions show good repeatability over time within the same location, whereas the *ex vivo* unperfused state drastically changes with time. Histological evaluations of the samples over time suggest that structural integrity was maintained in the perfused state but that cellular dissociation was more severe in the unperfused condition.

Since human's can detect differences in force as small as 10%, it is clear that *ex vivo* testing alone is not sufficient to accurately characterize the mechanical behavior of soft tissues. After minor modifications (changes in perfusate and pressure as suggested by histology) are applied, the *ex vivo* perfusion system is one method for obtaining the desired results in an accessible, ethical, and controlled manner.

This work has been supported by a grant from the US Army: contract number DAMD 17-01-1-0677.

Appendix B: selected CVs and BioSketches

Dawson, Steven L., M.D.

Howe, Robert D., Ph.D.

Ottensmeyer, Mark P., Ph.D.

Kerdok, Amy E., M.S

Petr Jordan, B.S.

BIOGRAPHICAL SKETCH

NAME	POSITION TITLE
Steven L. Dawson, M.D.	Program Lead, Medical Simulation, CIMIT

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	YEAR(s)	FIELD OF STUDY
State University of New York at Buffalo	B.A.	1974	Biology
Tufts University	M.D.	1978	Medicine
Medical-Surgical Intern, Newton-Wellesley Hospital		1978-1979	
Radiology Residency, Massachusetts General Hospital		1979-1982	
Imaging and Interventional Radiology Fellowship, Massachusetts General Hospital		1982-1984	

A. Positions and Honors

a. Positions and Employment

1982-1986 Radiologist, Waltham Hospital
1986-1990 Radiologist, Lahey Clinic
1990-Present Interventional Radiologist, Massachusetts General Hospital
1997-1999 Director, New Initiatives, Center for Innovative Minimally Invasive Therapy
1998-1999 Director, Education, Center for Innovative Minimally Invasive Therapy
1998-Present Program Lead, Medical Simulation, CIMIT, Massachusetts General Hospital
1994-2001 Assistant Professor, Harvard Medical School
2000- Visiting Scientist, Massachusetts Institute of Technology
2001- Associate Professor, Harvard Medical School

b. Honors

1974 Phi Beta Kappa
1992 RSNA Exhibit: Lee MJ, Dawson SL, Mueller PR. Percutaneous management of periportal biliary malignancies with metallic endoprostheses: results, technical problems and causes of failure. Certificate of Merit Award.
1990 Associate Editor, *Seminars in Interventional Radiology*
1994 Member, American College of Radiology Expert Panel on Interventional Radiology of ACR Task Force on Appropriateness Criteria
1994 Fellow, Society of Cardiovascular and Interventional Radiology
1997 Examiner, American Board of Radiology Subspecialty Examination in Vascular and Interventional Radiology
1995 Corresponding Fellow, Cardiovascular and Interventional Radiology Society of Europe
1997 External Reviewer, Biomedical Programs, Battelle / Pacific Northwest National Labs
1999 Session Chair and Lecturer, US Public Health Service and National Cancer Institute Joint Working Group on Image Guided Diagnosis and Treatment
2000 Partners Excellence Award
2003 First Annual Edward M. Kennedy Award for Health Care Innovation
2004 Tenth Annual Satava Award for unique vision and commitment to bringing technology to medicine
2004 Member, American College of Surgeons ad hoc committee on Simulators and Simulation for Surgical Education

B. Selected Peer-Reviewed Publications

Cotin SC, Dawson SL. CAML: a general framework for the development of medical simulation systems. Proceedings of SPIE 4037: 294-300, 2000.

Dawson SL, Cotin S, Meglan D, Shaffer DW, Ferrell MA. Desigining a computer-based simulator for interventional cardiology training [with editorial]. Catheterization and Cardiovascular Interventions, 51; 522-528, 2000.

Dawson, SL. A critical approach to medical simulation. Bulletin of the American College of Surgeons, 2002; 87(11): 12-18.

Cotin S, Stylopoulos N, Ottensmeyer M, Neumann P, Rattner D, Dawson S. Metrics for Laparoscopic Skills Trainers: The Weakest Link! Dohi T and Kikinis R, eds. Proceedings of MICCAI 2002, Laboratory Notes in Computer Science 2488, 35-43, Springer-Verlag, Berlin. 2002.

Stylopoulos N, Cotin S, Dawson S, Ottensmeyer M, Neumann P, Bardsley R, Russell M, Jackson P, Rattner D. CELTS: A clinically-based computer enhanced laparoscopic training system. Proceedings of 11th Annual Meeting, Medicine Meets Virtual Reality, Westwood JD, Hoffman HM, Mogel GT, *et al* eds. IOS Press 336-342, 2003.

Manivannan M, Cotin S, Srinivasan M, Dawson S. Real-Time PC based X-ray Simulation for Interventional Radiology Training. Proceedings of 11th Annual Meeting, Medicine Meets Virtual Reality, Westwood JD, Hoffman HM, Mogel GT, *et al* eds. IOS Press, 233-239, 2003.

Kalanovic D, Ottensmeyer MP, Gross J, Dawson SL. Independent testing of soft tissue visco-elasticity using indentation and rotary shear deformations. Proceedings of 11th Annual Meeting, Medicine Meets Virtual Reality, Westwood JD, Hoffman HM, Mogel GT, *et al* eds. IOS Press, pp 137-143, 2003

Kerdok A, Cotin SM, Ottensmeyer MP, Galea AM, Howe RD, Dawson SL. "Truth Cube: Establishing Physical Standards for Real Time Soft Tissue Simulation," Medical Image Analysis, vol. 7, pp. 283-291, 2003.

C. Ongoing Research Support

DAMD 17-99-2-9001, Dawson (PI) 10/1/99-9/30/01
DAMD 17-02-2-0006, and as amended: Dawson (PI) 10/1/01-9/30/07
Department of Defense
"Enabling Technologies for Medical Simulation"
The program examines fundamental aspects of mathematical, bioengineering and computer-based subsystems to develop effective medical learning systems
Role: PI

CDMRP Defense Health Related Programs, 00241063 Dawson, Howe (Co-PIs) 10/1/01-9/30/05
Department of Defense
"Advanced Soft Tissue Modeling"
This major grant examines in vitro and in vivo organ properties and develops constitutive laws to represent tissue behavior in computer-based simulations of medical procedures.
Role: Co-PI

BIOGRAPHICAL SKETCH

Provide the following information for the key personnel in the order listed on Form Page 2.
Photocopy this page or follow this format for each person.

NAME	POSITION TITLE
Robert D. Howe, Ph.D.	Gordon McKay Professor of Engineering

EDUCATION/TRAINING (*Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.*)

INSTITUTION AND LOCATION	DEGREE (*if applicable*)	YEAR(s)	FIELD OF STUDY
Reed College – Portland, OR	B.A.	1979	Physics
Stanford University – Stanford, CA	M.S.	1985	Mechanical Engineering
Stanford University – Stanford, CA	Ph.D.	1990	Mechanical Engineering

RESEARCH AND PROFESSIONAL EXPERIENCE: Concluding with present position, list, in chronological order, previous employment, experience, and honors. Include present membership on any Federal Government public advisory committee. List, in chronological order, the titles, all authors, and complete references to all publications during the past three years and to representative earlier publications pertinent to this application. If the list of publications in the last three years exceeds two pages, select the most pertinent publications. **DO NOT EXCEED TWO PAGES.**

Employment

1979-1981 Electronics Engineer, Kratos Display Systems. Los Gatos, CA.

1981-1983 Research Physicist, High Temperature Gasdynamics Laboratory, Stanford University

1984-1990 Research Assistant, Mechanical Engineering Dept. Stanford.

1990-1994 Assistant Professor of Mechanical Engineering, Harvard University.

1994-1997 Associate Professor of Mechanical Engineering, Harvard University.

1997-present Gordon McKay Professor of Engineering, Division of Engineering & Applied Sciences, Harvard University.

Selected Honors and Professional Service

National Science Foundation Young Investigator Award, 1993.

Best poster award, Sixth International Meeting of the Society for Minimally Invasive Therapy, Berlin (with William Peine), 1994.

Associate editor, *IEEE Transactions on Robotics and Automation*, 1994-1998.

Funding Review Panel Member, National Science Foundation, 1994, 2000.

Whitaker Foundation Biomedical Engineering Research Grant (career development award), 1995.

Chair and Organizer, Annual Symposium on Haptic Interfaces for Virtual Environment and Teleoperator Systems, ASME International Mechanical Engineering Congress and Exposition, 1996-1998 (with Susan J. Lederman).

Program Committee, International Symposium on Medical Robotics and Computer Assisted Surgery/MICCAI, 1994, 1995, 1997, 1998, 2000.

Program Committee, Frontiers of Engineering Symposium, National Academy of Engineering, Irvine, CA, Nov. 1998.

Selected Publications (from over 100 publications)

Samosky J, Burstein D, Grimson WE, Howe R, Martin S, Gray ML. Correlation of GAG distribution measured by dGEMRIC and spatially-localized mechanical stiffness in the human tibial plateau. *Journal of Orthopedic Research*, in press. (http://www.journals.elsevierhealth.com/periodicals/ortres/article/PIIS0736026604001202/fulltext)

M.P. Ottensmeyer, A.E. Kerdok, R.D. Howe, S.L.Dawson, "The Effects of Testing Environment on the Viscoelastic Properties of Soft Tissues," in S. Cotin and D.N. Metaxas, eds., *Proceedings of Medical Simulation: International Symposium - ISMS 2004*, Cambridge, MA, June 17-18, 2004, *Lecture Notes in Computer Science* vol. 3078, Springer-Verlag, pp. 9-18.

A.M. Galea and R.D. Howe, "Liver Vessel Parameter Estimation from Tactile Imaging Information," in S. Cotin and D.N. Metaxas, eds., *Proceedings of Medical Simulation: International Symposium - ISMS 2004*, Cambridge, MA, June 17-18, 2004, *Lecture Notes in Computer Science* vol. 3078, Springer-Verlag, pp. 59-66.

Y. Liu, A.E. Kerdok, R.D. Howe, "A Nonlinear Finite Element Model of Soft Tissue Indentation," in S. Cotin and D.N. Metaxas, eds., "*Proceedings of Medical Simulation: International Symposium - ISMS 2004*, Cambridge, MA, June 17-18, 2004, *Lecture Notes in Computer Science* vol. 3078, Springer-Verlag, pp. 67-76.T. Debus, T.-J. Jang, P. Dupont, and R. Howe, "Multi-Channel Vibrotactile Display for Teleoperated Assembly," International Journal of Control, Automation, and Systems 2(3):390-397, September 2004.

C.R. Wagner, S.J. Lederman, R.D. Howe, "Design and Performance of a Tactile Shape Display Using RC Servomotors," *Haptics-e* 3(4), August 2004.

T.J. Debus, P.E. Dupont, and R. D. Howe, "Contact State Estimation using Multiple Model Estimation and Hidden Markov Models," International Journal of Robotics Research 23(4–5):399-413, April–May 2004.

R.A. Beasley, R.D. Howe, and P.D. Dupont, "Kinematic error correction for minimally invasive surgical robots," Proceedings of the IEEE International Conference on Robotics & Automation, New Orleans, April 26-May 1, 2004.

R.L. Feller, C.K.L. Lau, C.R. Wagner, D.P. Perrin, R.D. Howe, "The Effect of Force Feedback on Remote Palpation," Proceedings of the IEEE International Conference on Robotics & Automation, New Orleans, April 26-May 1, 2004.

C.K.L. Lau, C.R. Wagner, and R.D. Howe, "Compliant Background Subtraction Algorithms for Tactile Rendering," Proceedings of the 12th Symposium on Haptic Interfaces for Virtual Environment and Teleoperator Systems, Chicago, March 27-28, 2004, IEEE Computer Society Press.

J.W. Cannon, J.A. Stoll, S.D. Selha, P.E. Dupont, R.D. Howe, and D.F. Torchiana, "Port Placement Planning in Robot-Assisted Coronary Artery Bypass," *IEEE Transactions on Robotics and Automation* 19(5): 912-17, October 2003.

Cannon JW, Howe RD, Dupont PE, Triedman JK, Marx GR, del Nido PJ. "Application of robotics in congenital cardiac surgery," *Seminars in Thoracic and Cardiovascular Surgery - Pediatric Cardiac Surgury Annual* 6:72-83, 2003.

A.E. Kerdok, S.M. Cotin, M.P. Ottensmeyer, A.M. Galea, R.D. Howe, and S.L. Dawson, "Truth Cube: Establishing Physical Standards for Real-Time Soft Tissue Simulation," *Medical Image Analysis* 7(3):283-91, September 2003.

R. A. Beasley and R.D. Howe, "Tactile Tracking of Arteries in Robotic Surgery," Proceedings of the IEEE International Conference on Robotics & Automation, Washington, DC, May 11 - 15, 2002, pp. 3801-6.

T. Debus, T.-J. Jang, P. Dupont and R. Howe, "Multi-channel vibrotactile display for teleoperated assembly, Proceedings of the IEEE International Conference on Robotics & Automation, May 11 - 15, 2002, pp. 592-7.

C. R. Wagner, N. Stylopoulos, and R. D. Howe, "The Role Of Force Feedback In Surgery: Analysis of Blunt Dissection," in Proceedings of the 10th Symposium on Haptic Interfaces for Virtual Environment and Teleoperator Systems, Orlando, March 24-25, 2002, IEEE Computer Society Press, pp. 73-79.

S. S. Park, R. D. Howe, and D. F. Torchiana, "Virtual Fixtures for Robot-Assisted Minimally-Invasive Cardiac Surgery," in W. J. Niessen and M. A. Viergever, eds., Proc. Fourth International Conference on Medical Image Computing and Computer-Assisted Intervention – MICCAI 2001, Utrecht, The Netherlands, 14-17 October 2001, Lecture Notes in Computer Science Vol.1679, Springer, Berlin, p. 1419-20.

S. Selha ,P. Dupont, R.D. Howe, and D. Torchiana, "Optimal Port Placement in Robot-Assisted Coronary Artery Bypass Grafting," *Fourth International Conference on Medical Image Computing and Computer-Assisted Intervention*, Utrecht, The Netherlands, 14-17 October 2001.

Wellman, P.S, Dalton, E.P., Krag, D., Kern, K.A., Howe, R.D. "Tactile Imaging of Breast Masses: First Clinical Report," *Archives of Surgery* 136(2):204-08 Feb. 2001.

NAME	POSITION TITLE
Mark P. Ottensmeyer, Ph.D.	Lead Investigator, Simulation Group, CIMIT, MGH Instructor, Harvard Medical School

EDUCATION/TRAINING (Begin with baccalaureate or other initial professional education, such as nursing, and include post-doctoral training.)

INSTITUTION AND LOCATION	DEGREE (IF APPLICABLE)	YEAR(S)	FIELD OF STUDY
McMaster University, Hamilton, Ontario, Canada	B.Eng.Mgt	1994	Mechanical Engineering and Management
Massachusetts Institute of Technology, Cambridge, MA, USA	M.S.M.E.	1996	Mechanical Engineering
	Ph.D.	2001	Mechanical Engineering

RESEARCH AND PROFESSIONAL EXPERIENCE: Concluding with present position, list, in chronological order, previous employment, experience, and honors. Include present membership on any Federal Government public advisory committee. List, in chronological order, the titles, all authors, and complete references to all publications during the past 3 years and to representative earlier publications pertinent to this application. If the list of publications in the last 3 years exceeds two pages, select the most pertinent publications. PAGE LIMITATIONS APPLY. DO NOT EXCEED THREE PAGES FOR THE ENTIRE BIOGRAPHICAL SKETCH PER INVESTIGATOR.

Research & Professional Experience

1991-1993 (summers) Research Assistant, McMaster University, Canada. Performed wind-tunnel experiments on electrical transmission line models to study transmission line galloping phenomenon. PI: Prof. Ozden F. Turan.

1993-1994 (summers) Research Assistant, Flexible Manufacturing Systems Laboratory, McMaster University, Canada. Developed power-up calibration system for AdeptOne industrial robot. PI: Prof. Hoda ElMaraghy.

1994-1996 Research Assistant, Human-Machine Systems Laboratory, M.I.T. Conducted research into and designed experiments on human performance in teleoperated surgery exercises with system time delays. PI: Prof. Thomas B. Sheridan.

1996-1998 Research Assistant, Haptics Group, Artificial Intelligence Laboratory, M.I.T. Developed thermal feedback device for virtual environment touch interface. PI: Dr. J. Kenneth Salisbury

1998-2001 Research Assistant, Haptics Group, Artificial Intelligence Laboratory, M.I.T. Developing minimally invasive surgical instruments for measuring mechanical properties of living organ tissues, performing in vitro and in vivo measurements. PI: Dr. J. Kenneth Salisbury

2001 Associate in Research, Harvard Medical School

2001-present Research Fellow, Massachusetts General Hospital

2001-present Instructor, Harvard Medical School

2001-present Lead Investigator, Simulation Group, CIMIT, Massachusetts General Hospital. Developing minimally invasive surgical instruments for measuring mechanical properties of living organ tissues, performing in vitro and in vivo measurements, designing simulators for medical/surgical training. P.I. Dr. Steven Dawson

Honors

1989 Ontario Scholarship
Sir Isaac Newton Physics Contest, Book award

1990 S.L. Squire Scholarship, McMaster University
Harry Lyman Hooker Scholarship, McMaster University

1991 Whidden Hall Residence Scholarship, McMaster University
Harry Lyman Hooker Scholarship, McMaster University

1992 Shell Canada Series Scholarship, McMaster University
Ray Lawson Scholarship, McMaster University

1993 Shell Canada Series Scholarship in Engineering and Management, McMaster University

Ray Lawson Scholarship, McMaster University
1994-'96 Post Graduate Scholarship A, National Sciences and Engineering Research Council, Canada (declined)
1996-'98 Post Graduate Scholarship B, NSERC, Canada
2003 Edward M. Kennedy Award for Health Care Innovation

Society Memberships
Sigma Xi, The Scientific Research Society, Full Member, 1995-present
ASME, Associate Member, Associate Member, 1996-present

Publications
Refereed journal papers:
Ottensmeyer, Mark P. TeMPeST 1-D: an instrument for measuring solid organ soft tissue properties. Experimental Techniques, vol. 26, no. 3, 28-50, May/June 2002.
Kerdok, Amy E., Cotin, Stephane M., Ottensmeyer, Mark P., Galea, Anna M., Howe, Robert D., Dawson, Steven L. Truth Cube: Establishing Physical Standards for Real-Time Soft Tissue Simulation. Medical Image Analysis, vol. 7, 283-291, 2003.
Konofagou, Elisa E., Ottensmeyer, Mark P., Agabian, Sue, Dawson, Steven L., Hynynen, Kullervo. Estimating localized oscillatory tissue motion for the assessment of the underlying mechanical modulus. Ultrasonics, vol. 42, 951-6, 2004.

Conference papers:
Ottensmeyer, M.P.; Salisbury, J.K. Jr. In Vivo Data Acquisition Instrument For Solid Organ Mechanical Property Measurement. Proceedings of the Medical Image Computing and Computer-Assisted Intervention 4th International Conference, MICCAI 2001, Utrecht, The Netherlands, pp975-982. 14-17 Oct 2001.
Bruyns, Cynthia, Ottensmeyer, Mark. Measurements of Soft-Tissue Mechanical Properties to Support Development of a Physically Based Virtual Animal Model. MICCAI 2002. Proceedings of the Medical Image Computing and Computer-Assisted Intervention 5th International Conference, Tokyo, Japan, pp282-289. 25-28 Sept 2002.
Cotin, Stephane, Stylopoulos, Nicholas, Ottensmeyer, Mark, Neumann, Paul, Rattner, David, Dawson, Steven. Metrics for Laparoscopic Skills Trainers: The Weakest Link!. MICCAI 2002. Proceedings of the Medical Image Computing and Computer-Assisted Intervention 5th International Conference, Tokyo, Japan, pp35-43. 25-28 Sept 2002.
Kalanovic, Daniel, Ottensmeyer, Mark P., Gross, Joachim, Buess, Gerhardt, Dawson, Steven L. Independent testing of soft tissue visco-elasticity using indentation and rotary shear deformations. Proceedings of Medicine Meets Virtual Reality 11, Newport Beach, CA. IOS Press. pp137-143. Jan 22-25 2003
Stylopoulos, N., Cotin, S., Dawson, S., Ottensmeyer, M., Neumann, P., Bardsley, R., Russell, M., Jackson, P., Rattner, D. CELTS: A clinically-based Computer Enhanced Laparoscopic Training System. Proceedings of Medicine Meets Virtual Reality 11, Newport Beach, CA. IOS Press. pp336-342. Jan 22-25 2003

Other publications:
Ottensmeyer, Mark Peter. Telerobotic Surgery: Feedback Time Delay Effects on Task Assignment. Master's Thesis in Mechanical Engineering at the Massachusetts Institute of Technology. © M.I.T., 1996.
Ottensmeyer, Mark Peter. Minimally Invasive Instrument for In Vivo Measurement of Solid Organ Mechanical Impedance. Doctoral Thesis in Mechanical Engineering at the Massachusetts Institute of Technology, © M.I.T., 2001.

Amy Elizabeth Kerdok

6 Craigie Circle Suite 41
Cambridge, MA 02138

Email: kerdok@fas.harvard.edu
web:http://hrl.harvard.edu/~kerdok/

Tel: (617) 308-2248
Fax: (617) 495-9837

Objective: Management or research position in the biomedical engineering or health sciences fields beginning January 2006.

Education

HARVARD UNIVERSITY — Cambridge, MA
Expected 2005

- Candidate for Ph.D. in Engineering Sciences, Division of Engineering and Applied Sciences, Biomechanics focus
- Enrolled in MIT/Harvard Health Science and Technology (HST) program for Medical Engineering/Medical Physics which includes approx. 1 year of medical coursework and 3 months of clinical clerkship

MASSACHUSETTS INSTITUTE OF TECHNOLOGY — Cambridge, MA
Sept. 1999

- MS, Mechanical Engineering, Biomehanics focus

RENSSELAER POLYTECHNIC INSTITUTE — Troy, NY
May 1997

- BS, Biomedical Engineering (*summa cum laude)*; Concentration: Mechanical engineering; Minor: Management

Research Experience

RESEARCH ASSISTANT: Harvard University Biorobotics Laboratory; Soft Tissue Biomechanics — Cambridge, MA
2000-present

- Designed and constructed soft tissue material property testing devices, finite element modeling of soft tissue behavior, clinical data collection and analysis
- Supervised undergraduate projects in biomedical engineering: conducted weekly meetings, provided thesis guidance, managed 40 hour/week x 2 undergraduate projects related to my work, helped with paper and presentation writing

RESEARCH ASSISTANT: MIT's Leg Laboratory and Harvard University's Concord Field Station; Sports Biomechanics — Cambridge, MA
1998-2000

- Experimental apparatus design and construction, human experimentation, data analysis, modeling the energetic and mechanical parameters of running

INTERN: Harvard Medical School's New England Regional Primate Center department of Cardiovascular Medicine with Dr. Stephen Vatner — Southboro, MA
Summer 1994

- Assisted in open heart animal surgeries, ran animal experiments on left ventricular hypertrophy dogs

Industrial Experience

PROJECT ENGINEER: ACT Medical Inc. (now MedSource Inc.) — Newton, MA
2000

- Managed and co-managed team projects, designed and developed various medical products (concept, prototyping, testing, quality, manufacturing), wrote proposals, managed project budgets and timelines, customer relations, consultation

RESEARCH TECHNICIAN (CO-OP): Howmedica Inc. (now Stryker) in Performance Engineering R&D — Rutherford, NJ
Summer 1995

- Operated MTS 810 and 407 controller single axis dynamic testing machines, designed orthopedic testing fixtures and molds (ISO, ASTM, and FDA standards)

Teaching Experience

HARVARD UNIVERSITY: Teaching Fellow

ES51 "Computer-Aided Machine Design" — Cambridge, MA, 2002, 2003

- Developed and ran the laboratory curriculum to teach undergraduate students engineering design via SolidWorks and computer-controlled milling machines (using CamWorks), managed undergraduate teaching fellows

ES149 "Muscles, Reflexes, and Locomotion" — Spring 2001

- Conducted weekly review sections, graded problem sets

Leadership Experience

MENTORING

- HST Biomatrix Mentoring Program: Includes graduate and undergraduate biomedical engineering students, and members of industry and academia — 2002-present
- Harvard College Science Mentoring Program for Women: graduate women in science are matched up with sophomore women — 2002-2003

SELECT COMMITTEES AND ELECTED POSITIONS

- HST Medical Engineering/Medical Physics Admissions committee: read applications, conduct interviews, select incoming class of ~20 students — 2001-present
- HST Education for Professionalism, Ethics and Responsible Conduct in Science (EPERC's) Task Force: helped draft a plan to bring ethics and professionalism into HST courses, web research to apply for grant to make plan a reality — 2004-present
- Student Representative for the Rensselaer Archer Center for Student Leadership: Organized Anderson Consulting Leadership conference — 1996
- Rensselaer Chapter of Pi Beta Phi Executive Board: Housing Committee Representative (worked with school to develop and fund a house for 60 women), Membership Chairman (developed alumnae database and semiannual newsletter) — 1995-1996

ACTIVITIES

- Harvard University Cycling Association: Team Captain (2003-4), Club President and MVP (2004), Collegiate National Championship Division 1 competitor (2002-4) — 2002-present
- Rensselaer Varsity Soccer, Most Dedicated, UCAA All-Academic team, Captain — 1993-1996

Computer Skills

- MATLAB, SolidWorks, CamWorks, ABAQUS (FEM), MS Visual Basic, MS Word, MS Excel, MS Powerpoint

Selected Awards & Honors

- Program Committee for International Symposium on Medical Simulation — 2004
- Faculty Achievement Award, Rensselaer Polytechnic Institute — 2003
- Harvard University Certificate of Distinction in Teaching — 2001, 2003
- Whitaker Fellowship, for advanced studies in Biomedical Engineering — 1997-2003
- Sigma Xi (national research honor society) — Inducted 1998
- Livingston W. Houston Citizenship Award, Rensselaer Polytechnic Institute — 1997
- Paul B. Diach Award, top biomedical student, Rensselaer Polytechnic Institute — 1997
- Tau Beta Pi (national engineering honor society) — Inducted 1996
- Founder's Award for Excellence, Rensselaer Polytechnic Institute — 1995
- Rensselaer Alumni Scholarship — 1993
- Rensselaer Polytechnic Institute medal (mathematics and science scholarship) — 1992

Publications and Patents

JOURNAL ARTICLES

Kerdok, A. E., Cotin, S. M., Ottensmeyer, M. P., Galea, A. M., Howe, R. D. & Dawson, S. L. 2003 Truth Cube: Establishing Physical Standards for Real Time Soft Tissue Simulation. *Medical Image Analysis* **7**, 283-291.

Kerdok, A. E., Biewener, A. A., McMahon, T. A., Weyand, P. G. & Herr, H. M. 2002 Energetics and Mechanics of Human Running on Surfaces of Different Stiffnesses. *Journal of Applied Physiology* **92**, 469-478.

REFEREED CONFERENCE PAPERS

Kerdok, A. E., Socrate, S. & Howe, R. D. 2004 Soft Tissue Modeling and Mechanics. In *American Society of Biomechanics Annual Meeting 2004* (ed. M. Bottlang & S. M. Madey). Portland, OR. **(poster presentation)**

Ottensmeyer, M. P., Kerdok, A. E., Howe, R. D. & Dawson, S. L. 2004 The Effects of Testing Environment on the Viscoelastic Properties of Soft Tissues. In *Second International Symposium on Medical Simulation* (ed. S. Cotin & D. Metaxas), pp. 9-18. Boston, MA: Springer Verlag. **(oral presentation)**

Liu, Y., Kerdok, A. E. & Howe, R. D. 2004 A Nonlinear Finite Element Model of Soft Tissue Indentation. In *Second International Symposium on Medical Simulation* (ed. S. Cotin & D. Metaxas), pp. 67-76. Cambridge, MA: Springer Verlag. **(poster presentation)**

Kerdok, A. E. & Howe, R. D. 2003 A Technique for Measuring Mechanical Properties of Perfused Solid Organs. In *ASME Summer Bioengineering Conference*. Key Biscayne, FL. **(poster presentation)**

Kerdok, A. E., Cotin, S. M., Ottensmeyer, M. P., Galea, A. M., Howe, R. D. & Dawson, S. L. 2001 Truth Cube: Establishing Physical Standards for Real Time Soft Tissue Simulation. In *International Workshop on Deformable Modeling and Soft Tissue Simulation* (ed. E. Keeve). Bonn, Germany. **(oral presentation)**

THESES

Kerdok, A. E., 1999. Energetics and mechanics of human running on surfaces of different stiffnesses. MS, Mechanical Engineering, Massachusetts Institute of Technology Cambridge.

PATENTS

Walczyk, D. F. & Kerdok, A. E. 2002 Mechanical Weight Bearing Indicator for the Foot, pp. US 6,405,606 B1: Rensselaer Polytechnic Institute.

Petr Jordán

Harvard University
Division of Engineering and Applied Sciences
29 Oxford Street, Pierce Hall
Cambridge, MA 02138
(617) 496-9098
pjordan@fas.harvard.edu
http://people.deas.harvard.edu/pjordan/

6 Craigie Circle #24
Cambridge, MA 02138
(617) 864-1066

EDUCATION

- **Harvard University**, Cambridge, MA. (August 2003 – present)
  Ph.D. candidate in Engineering Science.
  Medical Engineering and Medical Physics student in the Harvard/MIT Division of Health Sciences & Technology.
- **Lipscomb University**, Nashville, TN. (August 1998 – May 2002)
  Bachelor of Science. Major in Computer Engineering. Minor in Applied Mathematics.
  Senior thesis: *DSP-Based Real-Time Noise Cancellation for SQUID Biomagnetometers.*

RESEARCH INTERESTS

Medical Imaging and Vision, Tissue Mechanics, Signal and Image Processing, Graphics and Scientific Visualization.

RESEARCH PROJECTS

- Current research in soft tissue mechanics.
  Advisor: Robert D. Howe, Harvard Biorobotics Laboratory.
  3D ultrasonic imaging, optical flow deformation tracking, finite element modeling.
  (July 2003 – present)
- Development of real-time DSP-based noise cancellation for SQUID biomagnetometers.
  Advisor: Alan L. Bradshaw, Vanderbilt University, Department of Surgery.
  Signal processing, real-time system programming, circuit and cancellation coil design.
  (August 2002 – June 2003)
- Measurement of gastrointestinal magnetic fields with SQUID biomagnetomers.
  Advisor: Alan L. Bradshaw, Vanderbilt University, Department of Surgery.
  Signal acquisition and SQUID maintenance, investigation of the effects of diabetes on signal spectral content. (August 2001 – August 2002)

WORK EXPERIENCE

- **Research Assistant**, Biorobotics Laboratory, Harvard University
  (July 2003 – present)
- **Biomedical Engineer**, Department of Surgery, Vanderbilt University
  (June 2002 – June 2003)
- **Computer Assistant**, Information Services, Lipscomb University
  (August 1998 – May 2002)

REFERENCE

Available on request.

REFERENCES:

Febvay, S. (2003). Massachusetts Institute of Technology. Master of Science.